The American Journal of Medicine

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The American Journal of Medicine

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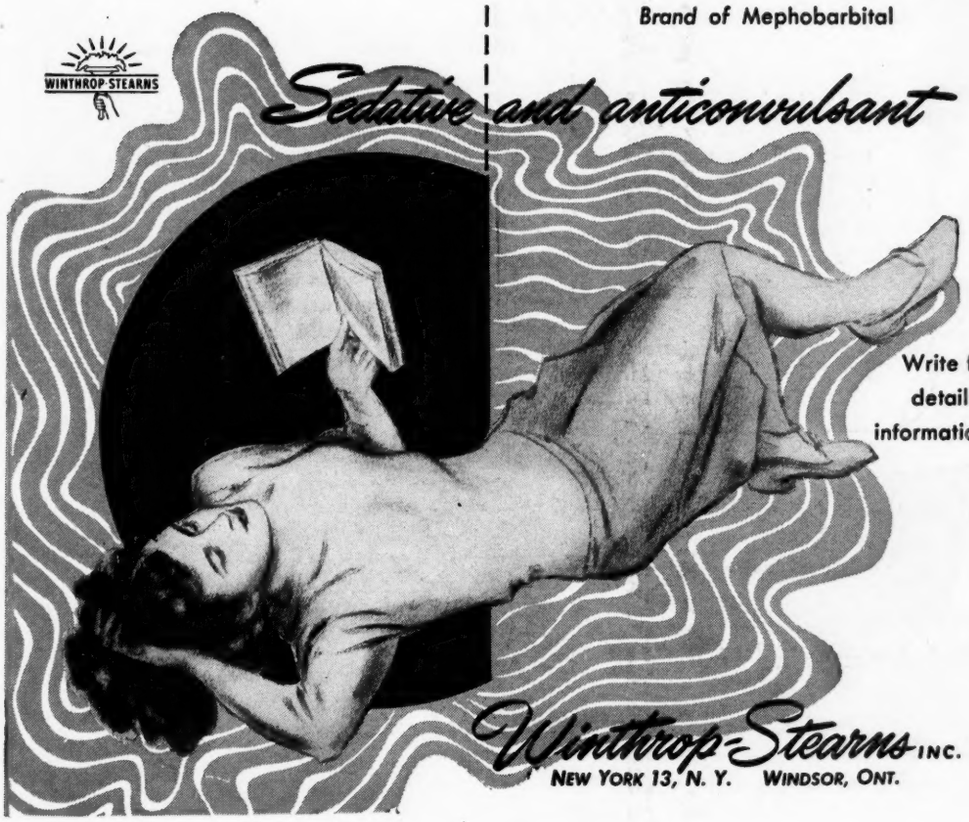

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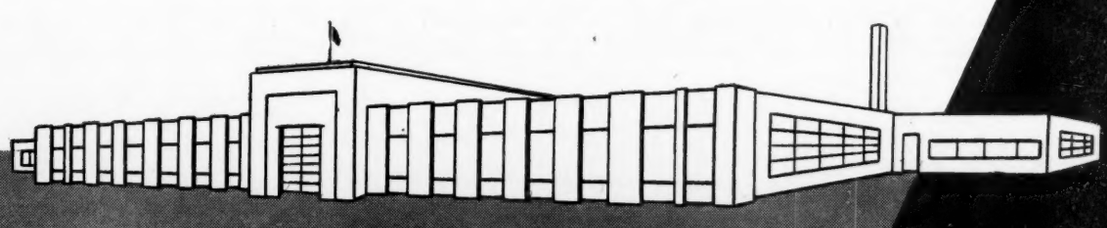

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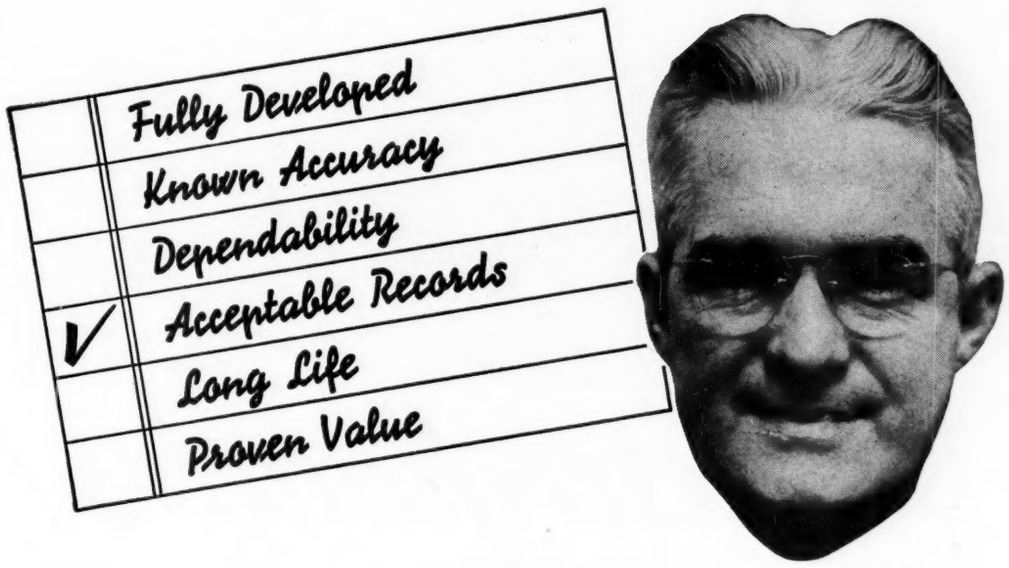

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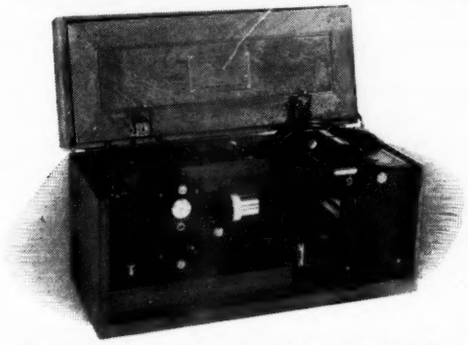

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1. Canada M. A. J. 54:283 (Mar.) 1946.
2. J. South Carolina M. A. 44:17 (Jan.) 1948.

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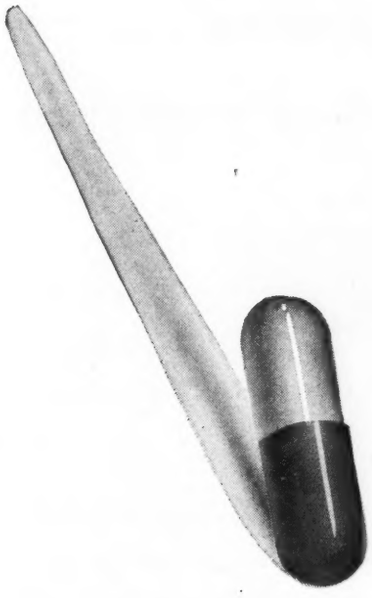

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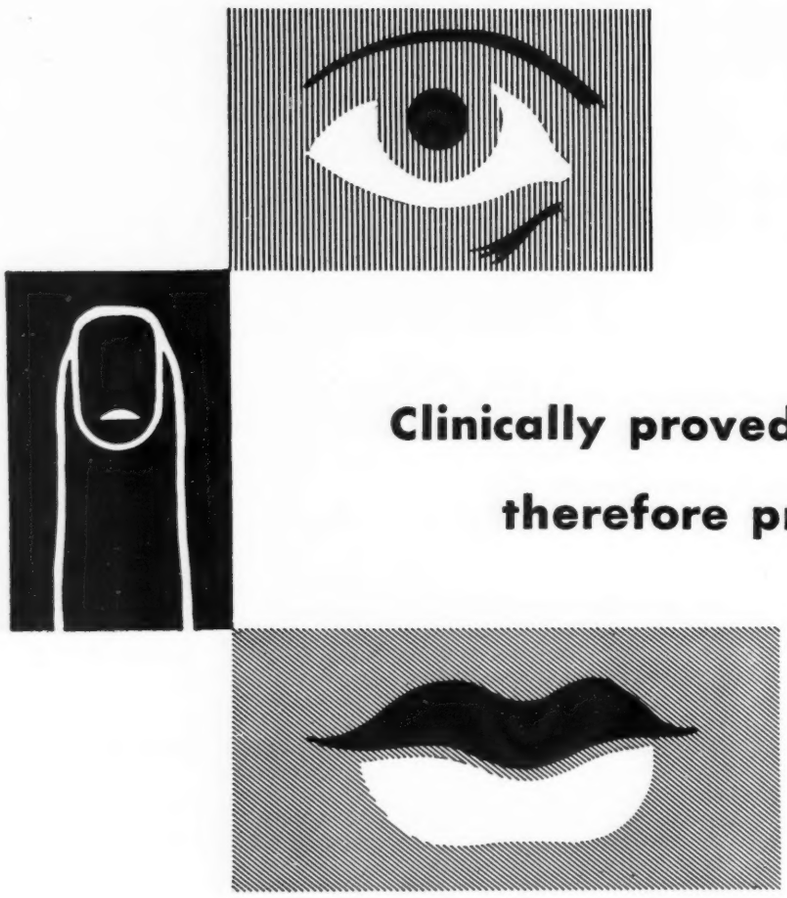

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In addition to the weight reduction of 118 pounds and the concurrent lowering of blood pressure, a remarkable improvement is reported in the patient's mood and outlook. Earlier nervousness and fears have vanished.

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*only 21 per cent of persons consuming average diets obtain protective quantities of vitamins.**

Were this serious indictment of four out of five menus based on supposition it might well be questioned. However, it is not conjecture, but has been arrived at by analysis of recorded diets of 3336 persons as well as by actual chemical assay of the dietaries of 71 persons. In summing up the study the authors state: "Any conclusions as to the deficiencies present, when drawn from the analysis of the food of the test group, may be regarded as conservative in relation to the nation as a whole."

However, poor selection in the choice of food is only one factor contributing to this situation. The vitamin content of many foods as prepared for consumption is often considerably less than the vitamin content when first produced.

Handling of vegetables and fruits in picking, storing, packing and shipping frequently reduces vitamin content. As much as eighty per cent of ascorbic acid and ninety per cent of thiamine may be lost through overcooking or prolonged soaking.

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*Lockhart, E. E.: Harris, R. S.; Tapia, E. W.; Lockhart, H. S.; Nutter, M. K.; Tiffany, V., and Nagel, A. H.: J. Diet. Assn. 20:742 (Dec.) 1944.

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**Krasno, L., Karp, M., and Rhoads, P. S., (1948), Inhalation of Dust Penicillin, Ann. Int. Med., 28: 607-617, March.*

(a) Discharge chamber is attached either to (b) Mouthpiece or (c) Nosepiece, for use with (d) Abbott Sifter Cartridge.

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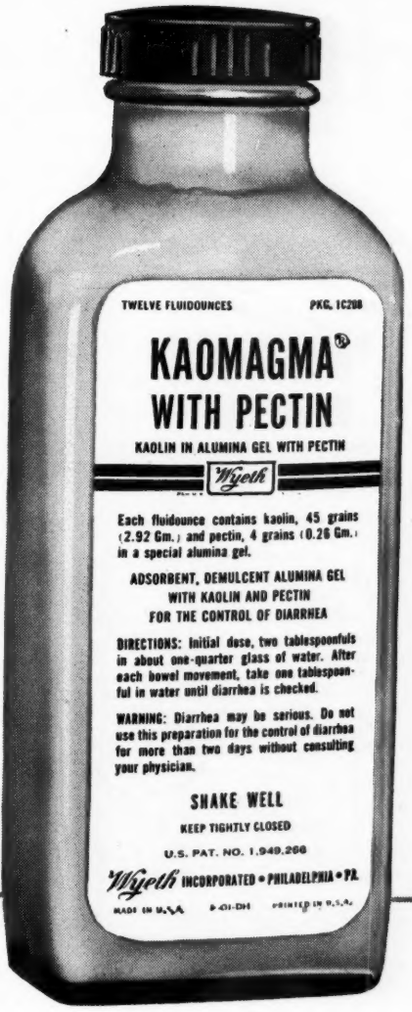

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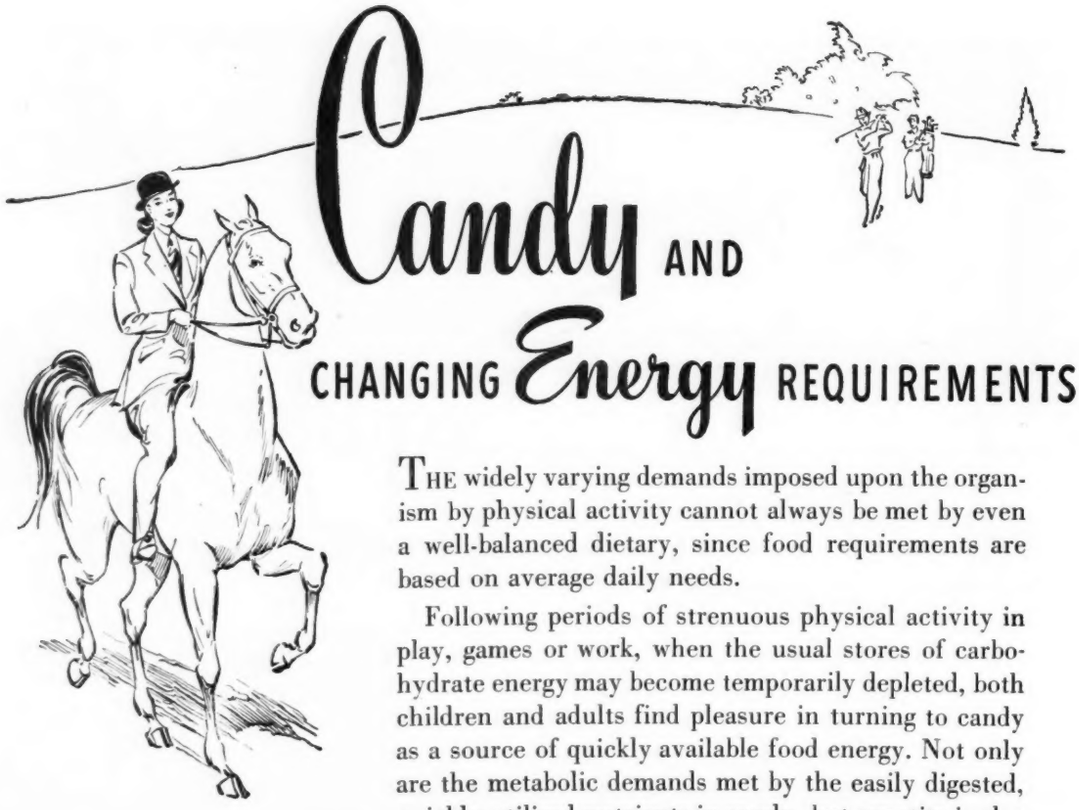

THE widely varying demands imposed upon the organism by physical activity cannot always be met by even a well-balanced dietary, since food requirements are based on average daily needs.

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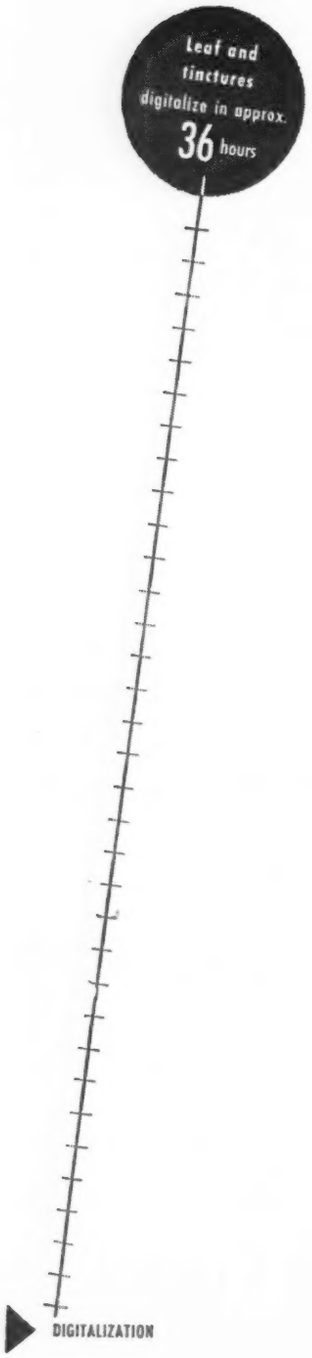

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The American Journal of Medicine

VOL. V AUGUST, 1948 No. 2

Editorial

Problems of Convalescence

ACCORDING to Stedman's Medical Dictionary the word convalescence (growing strong) refers to the time that elapses between the termination of a disease and the patient's complete restoration to health. The simple finality of that statement invites discussion. Its implied supposition that "a disease" is something a man "gets" or "has" maintains the primitive concept that he himself is a victim of olympian wrath. That he may be an important causal factor in his own malady the statement completely overlooks. One might as well ask when does a disease actually begin as to judge when it terminates. The pathologic events which occur between two successive states of health form a continuum. The course or curve in recovery from the onset of disease to the stated cure varies greatly with different persons. In some cases the curves of disease from onset to peak and through the descent are rapidly described. In others every variation in form and speed appears. Those who dally in regaining health and in the ability to return to their previous life-setting deserve special scrutiny. No doubt various facts and motives determine why slow recoverers are slow. Of course, many subjects with early deterioration of tissues such as liver, kidney or arteries, as well as those with rheumatoid arthritis and similar disabilities, should hardly be classed as convalescents. They clearly belong in the growing ranks of victims of chronic disease whose chances for ultimate recovery are what they may be. A good deal can often be done to make resumption of work fairly successful for shorter or longer periods of time. This type of fixed tissue disease rarely moves in the direction of biologic recovery. But even with great physical handicaps certain persons may achieve superb capacity for work. Deaver, Rusk and others have shown that the patients' effectiveness may be maintained for remarkably long periods by proper, diet training and point of view.

In many convalescent homes the most satisfactory patients, as far as recovery is concerned, are those whose maladies arise in the organs equipped with smooth muscle which is motivated by the autonomic nervous system. These include the whole field of the neuroses, for example, peptic ulcer, thyroid disease, asthma, enteritis and essential hypertension.

In Homeric times the Greeks used to speak of two varieties of medicine—profane and sacred. The former dealt with sewing up the wounds of a warrior, setting broken bones and treating any ailment caused by explainable physical forces. Sacred medicine or magic, on the other hand, had to be called upon for maladies whose concealed inner mechanism could not be perceived or directly dealt with by tangible methods. The former has come down the ages to end in modern surgery and physiotherapy for physical rehabilitation. Sacred medicine or magic has turned into contemporary psychotherapy. Today the combined technics are expressed in that presently overworked word, "psychosomatic."

And this brings us to the specific problems of convalescence and convalescent care. The question has often been raised

as to what sort of regimen should be provided at convalescent homes. In the first place, the term "home" carries a maternal connotation of "being taken care of," a continuation of the protective nursing just terminated in the general hospital. If the patient is well enough to leave that phase of his illness, he should be weaned as promptly as possible. A better name for the modern convalescent home would be "Recovery Training Institute." The effort of all concerned with the patient's ultimate recovery should be to help him as little and as indirectly as possible within the limits of good sense. One of the remarkable achievements at the Bellevue Clinic has been the education of patients to help themselves and to become independent of their former aids. They are taught self-sufficiency in the face of handicaps.

There are times, too, when patients flee from apparently insoluble family troubles "just to get away from it all." Such cases derive scant benefit from the three weeks of sunlit and well fed loneliness among strangers, agoraphobia and anticipated terror at the idea of returning to their unsolved problems. These individuals might better have settled the home conflict first. It probably led to the acute illness or general collapse which called for a convalescent period. After such a settlement the healing virtues of fresh air, sunshine, good food and rest might have produced more rapid and complete rehabilitation. The recovering patient is in a tough spot indeed, one which often defies a first-class social service worker. A large number of patients who avoid the guidance of a well trained and wise physician use a Recovery Hospital as an escape from the intolerable family situation. Many others are without funds and have nowhere to go when they leave the institution, which therefore is often forced to act as a hostel for lost and stranded wayfarers. And so the medical problems for which the patients seek final relief become submerged beneath waves of personal and social relationships and world economics.

Medical men have always realized that when a new remedy like penicillin appears, which "cures" a definite disease in the mass, the intimate relationship between patient and doctor, which Jung calls "le participation mystique," tends to diminish. Moreover, the shortened period of illness, which often results from new drugs, hardly permits more than a "how-do-you-do, good-bye" relationship. In preventive medicine there is not much personal interchange between the Board of Health doctor and his 5,000 vaccinees.

Treatment of the acute phase of disease in a general hospital, where tangible ills are handled in heroic fashion, has much in common with the Greek concept of profane medicine. In sharp contrast, the recovery phase of disease should call forth the special technics which have now been developed to perform the work of sacred medicine. The patient, exhausted by his bout of acute sickness, feels unlike his former self; he is a strange and unaccustomed pilot in his own conning tower. He finds himself doubtfully suspended between what went before and what lies ahead. He reaches for a guiding hand and should find one whose sensitive and powerful grasp provides exactly the correct proportions of direct help and insistence upon the achievement of self-help. In the recovery phase of disease, therefore, the physician should encompass all the skills of sacred and profane medicine with which to restore the patient to his original wholeness; short of that the patient will have learned to accept his residual handicap and find a way to carry on in spite of it.

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Clinical Studies

Pulmonary Paragonimiasis

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OBSERVATIONS of twelve cases of paragonimiasis among Filipino guerrillas hospitalized in a large general hospital on the island of Leyte are presented because the cases are of unusual interest and also because the disease may be encountered in the future in the United States where it has hitherto been practically non-existent. Miller and Wilbur in 1944 reported three cases, with mention of four others, in returning veterans.[6]

Paragonimiasis, also known by the terms pulmonary distomatosis, pulmonary distomiasis, parasitical hemoptysis, gregarinosis pulmonis, endemic hemoptysis and oriental lung fluke disease, is produced in man by the invasion of the trematode Paragonimus through the ingestion of infected raw or incompletely cooked crab or crayfish.

Paragonimiasis is widely distributed. The parasite was originally found in the lungs of a tiger in a zoo in Amsterdam, Holland, in 1877 and was described by Kerbert in 1878 and named Distoma westermani in honor of the director. In 1880 Mason in a letter described eggs in the sputum of a Chinese male and referred to a parasite in the lungs found by Ringer in still another patient. This fluke, sent to Cobbold, the recipient of Mason's letter, was named D. ringeri by Cobbold. Shortly afterward Baelz in Japan also discovered eggs in sputum and named the parasite D. poulmonale. In 1889 Leukart, comparing the worm of Baelz and the worm of Kerbert, found them quite similar except for minor differences. This conclusion has been widely accepted. In 1899 (Braun) the parasite was placed in a new genus, Paragonimus, and P. westermani was employed, commonly because of priority, synonymously for P. ringeri. This usage is not agreeable to those who favor the existence of several distinct species of the trematode.

Ward in 1894 found a fluke in a cat from Michigan but because of the possibility that the cat had been imported could not call it endemic to North America. Somewhat later that same year Kellicot found a similar fluke in a dog from Ohio and in 1908 Ward named it after Kellicot, P. kellicoti. Nakagawa in 1917 described the life cycle of the lung fluke in Japan and in 1934 Ameel worked out in detail the life cycle of the lung fluke in North America.

There has been considerable controversy among workers regarding differentiation of the species of Paragonimus. Ameel in 1934, after a careful study which implied the possibility of one species, stated that "in the absence of conclusive evidence either to support or contradict the work of Ward and Hirsch, it is believed advisable to recognize the species considered valid by them, namely, Paragonimus westermani, P. ringeri and P. kellicoti. Likewise P. compactus, recognized as a distinct species by Vevers, should be retained until it is restudied."

Paragonimiasis has been found in men and other mammals, including the cat, dog, hog, goat, fox, wolf, leopard, wild cat, panther, wolverine, beaver, mink, mongoose and civet cat. Although hyperendemic foci for man exist in the Far East, Japan, Korea, Formosa and the Philippine Islands, it is found elsewhere. The most recent publication, *Manual of Tropical Medicine* (National Research Council), states that the disease has been found in Africa (Belgian Congo, British Cameroons, French West Africa and Tripoli), Central China, French Indo-China, Manchuria, Samoan Islands,

Malay Peninsula, New Guinea, India (Assam, Bengal, Malabar, Madras and Presidency) and South America (Brazil, Peru, Ecuador and Venezuela). There is uncertainty as to the presence of the disease in the Netherlands Indies.

According to Khaw, the disease has been found in the United States in the cat, dog, hog, wild cat, goat and mink. Ohio, Minnesota, Wisconsin, California, South Carolina, Mississippi, New York and Kentucky have at times produced the infected animals. With the exception of California, where the infected cats and dogs were found in the oriental quarters of San Francisco and could possibly have been imported, it would appear that the remaining states can provide the intermediary hosts necessary for infection. Ameel in a survey found suitable crayfish and snails in Kentucky and Tennessee, none of which were infected, and he points out that although the disease is at present confined to domestic and fur-bearing animals in the Americas it must be looked upon as a potential human parasite.

The parasite, like all trematodes, has a complex life cycle. The egg is either coughed up in the sputum, passed in the feces or, less commonly, escapes by way of the ulcerated skin. It is rather large, oval, operculated, and yellow to dark brown in color. Its dimensions vary but, as generally given, measure 85 to 100 micra in length and 50 to 65 micra in width.

Upon reaching water development proceeds within a few weeks by hatching of miracidia which in turn penetrate snails of several species. Several months elapse for the transformation of miracidia through the stages of sporocysts, rediae and cercariae. Cercariae invade the second intermediate host, a crustacean (either a crab or crayfish of many species), and encyst in the muscles as metacercariae. Following the ingestion of an infected crab or crayfish, these are released in the alimentary tract which is penetrated in the region of the jejunum. After entrance into the peritoneal cavity the diaphragm is invaded, then the pleural cavities and eventually the lung where the majority of parasites mature.

The mature worm is dark reddish-brown in color and its shape is oval verging on the spherical. It measures 8 to 20 mm. in length and 5 to 9 mm. in width. While not actively motile outside the lung, movement of various portions of the worm can be observed when it is freshly removed from the tissue of the host. A thick skin of cuticle covering the worm is overlain with scale-like spines. There are two suckers, an oval terminal and a ventral just cephalad of the mid-portion of the body. The alimentary tract is rudimentary, consisting of pharynx and esophagus dividing into two intestinal ceca which end blindly at the caudal end. The testes lie on both sides of the midline posterior to the uterus which is centrally located opposite the branched ovary, slightly posterior. The excretory system consists of a large, elongated excretory sinus lying in the mid-axis of the body terminating in an excretory pore on the dorsal surface.

PATHOLOGY

The earliest lesions of paragonimiasis produced experimentally in the lungs of kittens and puppies according to Nakagawa may be seen three days after feeding as pin-head hemorrhagic spots which become dark red in fourteen days. Within twenty-one to twenty-five days pale cysts may be seen at the site of the petechiae. About forty-five days after feeding the cysts are dark red and are surrounded by leukocytes, round cells and erythrocytes. In another week a vacuole is present which may contain a worm but very often the worm has gone into the surrounding tissue. Ninety days after feeding the cysts are bluish-grey, the vacuole has increased in size and porridge-like material containing one or two mature worms may be present. The cyst wall may be intact or in communication with an air space, bronchus or pulmonary vein radical. Eggs may also be noted at this time either in the cyst or parenchyma of the lung where erythro-

cytes, leukocytes, epithelial cells and débris also are gathered. The bronchioles and bronchi may also be dilated, containing red cells, leukocytes and eggs.

Musgrave in 1907 described the autopsy findings in eight cases of paragonimiasis in the human. The lesions in these cases were massive and far advanced. Almost every organ with the exception of the stomach was involved. The diaphragm was involved in every case. The pleura, lungs, omentum, small intestine, large intestine and the surface of the liver beneath the capsule were affected in five or more of the eight cases. The pectoralis major and psoas muscles, the pericardium and heart, spleen, pancreas, appendix, kidney, bladder, scrotum, prostate and brain less frequently also contained typical lesions. He called special attention to the involvement of the superficial, subcutaneous and deep mesenteric nodes which in two cases had broken down in the axillary and in one case in the inguinal regions. Musgrave describes the characteristic lesion as a necrotic abscess, of a peculiar dull bluish-slate color with a definite wall made up of layers whose outer surface is connected with surrounding tissue and whose inner surface is a smooth membrane; an anchovy-like sauce material fills the cavity in which adult worms and eggs may or may not be present. Occasionally the central material may resemble ordinary pus or be caseous. Inflammatory reaction is generally absent surrounding the lesions.

In addition Musgrave described: (1) non-suppurative lesions found as adhesions between pleural surfaces which contained ova; (2) a tubercle lesion generally in the lung; (3) in loose connective tissue, as simple infiltration with ova or as hyperplasia containing ova or, when in the lung, as focal specific pneumonia lesions in which the presence of parasites and ova is variable; (4) a suppurative lesion resembling ordinary pyogenic lesions, frequently containing ova; (5) ulcerative lesions in the skin in association with breakdown of lymph nodes and also in the mucous membrane of the bronchi and the intestine. Such pathologic involvement can produce different clinical syndromes. As the cases indicate various pulmonary lesions may be encountered.

Clinical Findings. Clinically, the patient presents the picture of a slowly progressive pulmonary disease. Musgrave speaks of an acute form of the disease in which the course is rapidly downhill. It should be recalled that he was primarily interested in the pathology of the disease and that his cases occurred in prisoners over forty years ago. At that time and amidst such surroundings clinical histories were either meager or lacking. In addition, complicating conditions common to prisoners in that location, such as severe malnutrition, beri-beri and amebic dysentery, were coexistent.

The onset of symptoms in our patients varied from one week to thirty-four months prior to observation so that both early and late cases were seen. In all but one instance a definite history of fresh-water shellfish ingestion was obtained, but due to the frequent inclusion of shellfish in the diet it was not possible to determine the time relation of the onset of the first symptom to this exposure. The illness began insidiously in five patients following a febrile episode clinically diagnosed malaria but not confirmed by laboratory study. The incidence of malaria is so high in these regions that the patients' description of their illness and its response to antimalarial therapy prompt us to accept the diagnosis of malaria as probably correct. The introduction of the disease in these five patients was so similar that one wonders whether malaria specifically or as an acute debilitating febrile disease precipitated the appearance of the clinical symptoms of paragonimiasis. Three patients stated that they were feverish and chilly at the onset but that the fever cleared in a few days and a cough continued. In over one-half the patients, therefore, the onset was associated directly or indirectly with fever.

In all patients cough or hemoptysis, gradually increasing in severity, was the first symptom of the disease. The cough, at first dry and irritating, rapidly became

productive of sputum. The cough was present throughout the day and was increased by effort and fatigue. It was more marked in the early evening and early morning and in three patients it was especially prominent at night. The sputum characteristically contained flecks of dark blood. While hemoptysis was present in all patients, its onset varied; in some it appeared early, in others late and in two patients it did not appear until two years following the onset of the cough (Cases III and XI). Although more often tenacious, thin watery sputum was seen and the color varied from a yellow-white to frankly bloody. Dark greenish sputum was encountered only in those patients who had associated tuberculosis. The sputum from which ova were most frequently recovered was gelatinous, purulent, bloody and of a slightly sour odor in which were scattered dark brownish-red flecks resembling cigarette tobacco shreds. The amount of sputum produced daily ranged from 30 to 90 cc. and varied at times in the same patient.

Chest pain was present in all but one patient (Case II) during the course of illness. Pain was related to respiratory motion in only five patients, in the others it was described as deep in the chest, sticking, transient and shifting or increased by cough and activity. Rarely it could not be definitely localized.

Two-thirds of the patients complained of loss of weight, weakness and tiredness. These symptoms were difficult to evaluate as all patients carried out arduous duties at the onset of the disease and for some time thereafter, and their appearance in the majority of instances did not suggest weight loss. In only two histories (Cases I and X) could it be stated with reasonable accuracy that weight losses of 20 and 26 pounds had occurred. Dyspnea occurred in five patients, three of who had accompanying effusion; in the remaining two the parenchymal lesion was apparently responsible. Four patients complained of night sweats and in only one of these was fever detected during hospitalization. Gastrointestinal symptoms such as anorexia and vomiting were encountered occasionally. In two patients a history of hematemesis was present. Although we questioned both patients in great detail we could not be certain whether pulmonary or gastrointestinal bleeding had occurred; hepatomegaly and splenomegaly were not present in either case.

Two patients (Cases VIII and X) complained of pain in the extremities. We were not familar with Musgrave's findings at that time indicating involvement by the fluke of muscle and lymph nodes. Physical examination offered no adequate explanation for these symptoms, which gradually disappeared. Palpitation occurred in two patients with pleural effusion, in neither of whom were we able to demonstrate by physical examination, x-ray or electrocardiographic study any striking abnormality of the heart. (Table I.)

Physical Findings. The relative well being of these patients, with few exceptions, was noted by almost every observer. In spite of the history of prolonged cough and hemoptysis the majority of patients did not appear to be sick. The few who appeared ill on the first examination invariably were those patients who had fluid in their pleural cavity, but not all patients with empyema appeared sick in the sense associated with pyogenic empyema. Loss of weight, although prominent in the history, was frequently not apparent upon physical examination.

The temperature during hospitalization exceeded 102°F. in two cases (Cases IX and XI), ranging between 99 to 100°F. for more than seven days in Cases I and VI and was either normal or reached 100.2°F. for one to three days in the remainder throughout the months of hospitalization. Prolonged fever was associated with the presence of pleural fluid but fever was not present in all patients who had fluid.

Physical signs indicative of pulmonary disease were present in all of the patients at some time in their hospitalization prior to therapy. These findings were not constant and were at variance with those reported

by Bercovitz. A possible explanation for this difference may be that these patients were hospitalized and were examined more frequently over a course of many months. Râles were present in eleven of the twelve patients. These varied from fine to coarse in character and were heard in varying portions of the lungs. Musical, sibilant and sonorous râles were rarely heard. Characteristic signs of fluid were present in only two of these patients (Cases III and X).

There were no noteworthy findings referable to the heart; a very large, smooth, non-tender liver was palpable in three patients (Cases II, III and IV); firm, large spleens were present in two patients (Cases II and IV); no unusual adenopathy was encountered.

TABLE I

SYMPTOMS IN REPORTED CASES

Case No.	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Duration	24 mo.	6 mo.	24 mo.	1 wk.	8 mo.	16 mo.	8 mo.	3 mo.	12 mo.	18 mo.	33 mo.	34 mo.
Onset	Malaria; pain; hemoptyses	Cough	Malaria; cough	Acute fever; hemoptyses	Anorexia; cough; weakness	Fever; chills; hemoptyses	Cough; hemoptyses	Fever; cough; hemoptyses	Cough	Malaria; hemoptyses	Cough	Malaria; cough; chest pain
Cough	+	+	Nocturnal +	+	+	Nocturnal +	+	Nocturnal +	+	+	+	+
Hemoptyses	+	+	+	+	+	+	+	+	+	+	+	+
Chest pain	Not resp.	0	Resp.	Not resp.	Resp.	Resp.	Not resp.	Not resp.	Resp.	Not resp.	With cough	Resp.
Loss weight	+	0	±	0	+	+	±	0	0	+	+	+
Weakness	+	0	+	0	+	+	0	0	0	+	+	+
Fatigue	+	0	+	0	+	+	0	0	0	+	+	+
Dyspnea	0	0	+	0	+	0	0	0	0	+	+	+
Vomiting	0	0	+	0	0	0	blood	0	0	0	Blood	+
Palpitation	0	0	+	0	0	0	0	0	0	+	0	0
Pain in extremities	0	0	0	0	0	0	0	+	0	+	0	0
Anorexia	0	0	0	0	+	0	0	0	0	0	0	+
Night sweats	0	0	0	0	0	0	+	0	0	+	?	+

Laboratory Findings. The laboratory diagnosis of this disease depends upon the recognition of characteristic ova. Ova can be recovered from the sputum, feces, fluid of serous cavities and broken down infected lymph nodes. In our patients ova were found in sputum, feces and pleural fluid.

The type of sputum from which ova are most frequently recovered has been described previously; the presence of scattered brownish-red flecks, closely resembling cigarette tobacco shreds in sputum is reemphasized as especially indicative of accompanying ova. Although ova are easily identified when seen, staining will mask their presence. In Case XI, for example, twenty-four specimens were searched for tubercle bacilli before a drop of sputum was directly examined and ova of P. westermani were found in the second examination. Ova are not produced in the sputum regularly and in quantity so that examination of many specimens is required before it can be assumed that they are absent. Bercovitz mentions a case in which ten examinations were necessary before ova were recovered. We have had similar experiences. When few ova are excreted, concentration technics are most helpful. In suspicious cases when direct examination of the sputum is fruitless, five or more examinations by concentration technics should be done before concluding that the disease is not present.

Recovery of ova from the stool is more difficult. In seventy-one stool examinations in the twelve patients with positive sputum ova were recovered seven times (Cases I, II, V and VIII).

The pleural fluid in four patients varied from a thin, blood-tinged, serous fluid to a thick, creamy, purulent fluid. Yellowish curd-like particles were present throughout the fluid. Red cells only were identified in the blood-tinged fluid. A paraffin block of the purulent fluid revealed leukocytes in

various stages of degeneration, among which eosinophils were absent. All fluids were negative for organisms upon both smear and culture. Fourteen examinations were made in four patients (Cases III, V, IX and X) and in only one instance (Case X) were ova recovered on five occasions.

The changes noted in the blood counts in this series must be cautiously interpreted as the direct result of paragonimiasis since all patients had, in addition, at least one or more intestinal parasite and many had either observed malaria or had a history of recurrent malaria.

The average hemoglobin (Sahli) prior to therapy was 83 per cent, the average erythrocyte count was 4,300,000 per cu.mm. and the average leukocyte count was 11,300 per cu.mm. These findings check closely with Bercovitz's report of 78 per cent average hemoglobin and 4,303,000 per cu.mm. erythrocyte count in twenty patients. The hemoglobin ranged from 70 to 100 per cent and the red cell count from 3,100,000 to 5,400,000. Leukocytosis ranging from 15,000 to 21,000 was seen in every case in which fluid was present and was encountered twice in the absence of fluid. It seems probable that initial leukocytosis does not occur in the absence of complication, as values from 6 to 10,000 leukocytes were seen in patients whose duration of symptoms varied from one week to one year. Eosinophilia was present in all patients. We believe this finding was due to accompanying parasites commonly responsible for high eosinophilic values. Most authors state that paragonimiasis is not accompanied by eosinophilia. (Table II.)

Following the use of emetine and anthelmintics, there was a slight increase in the hemoglobin and red cell count and a decrease in the leukocyte count.

The erythrocyte sedimentation rate was elevated above 20 mm. per hour in ten patients. The highest level reached was 68 mm. per hour in a patient with hydrothorax and coexistent tuberculosis. The rate was always elevated in the presence of fluid. In five patients (Cases II, IV, V, VI and VII) it became normal prior to the administration of emetine therapy. In one case aspiration of fluid may have produced this result. In four patients (Cases I, V, XI and XII) elevation of the sedimentation rate occurred after treatment; in two such instances (Cases V and XII) tuberculosis was coexistent. In two patients (Cases III and VIII) the sedimentation rate decreased but was still elevated following treatment and in only one instance (Case X) was it normal both after removal of fluid and emetine administration.

Our data do not permit thorough evaluation of the sedimentation rate in this disease; the results were too widely scattered and the cases too few. It can be pointed out, however, that a normal sedimentation rate does not preclude the presence of ova in the sputum.

Transiently positive serologic tests were noted in four patients (Cases I, II, V and IX) both by the Kahn test and Wassermann reaction. The four patients concerned denied initial lesions and had no external manifestations of either syphilis or yaws. These equivocal reactions involving one-third of the patients stimulated serum protein studies. Seven patients (Cases I, II, III, V, VIII, IX and XI) showed an increase in serum globulin. Above 3.0 Gm. per cent most showed some fall in albumin, the total serum protein levels remaining within normal limits. (Table III.) Serum protein changes have been reported in many diseases, including tuberculosis, malaria and schistosomiasis. These diseases were present in four of the patients (Cases I, III, V and VII). Hepatic disease may have contributed to the serum protein changes in two instances. (Cases II and III.) In Cases VIII, IX and XI the serum protein variation could not be explained except as a result of paragonimiasis.

The urinary findings were normal in all patients.

Roentgenologic Observations. Eleven patients showed involvement of the lung in the initial x-ray of the chest. The twelfth subject (Case VIII) showed extremely heavy

TABLE II

HEMATOLOGIC FINDINGS

Case	Date	Hgb.	R.B.C. (million)	W.B.C.	Polys.	Lymphs.	Eosinophiles	E.S.R.	Other Parasites	Comments
I	8/30/45	...	....	.....	..	..	..	36	A. lumbricoides	
	9/11/45	...	....	8,800	54	14	32	..	Hookworm	
	9/24/45	90	4.65	8,000	52	27	21	29	T. trichiura	
	10/ 6/45	...	....	14,400	53	13	34	48	S. japonica	
	11/ 7/45	...	....	.....	..	..	..	15		
	11/16/45	80	4.2	9,600	62	38	14			
II	3/20/45	75	4.8	9,000	..	..	..	..	A. lumbricoides	
	5/17/45	85	4.2	8,000	62	38	..	13	Hookworm	
	9/ 1/45	...	....	6,200	46	42	12	..	E. histolytica	
	9/19/45	95	4.7	6,400	45	46	9	12	T. trichiura	
	9/24/45	...	....	7,200	48	41	11	4		
	10/21/45	...	....	8,400	64	24	12	14		
III	9/12/45	...	....	14,600	49	17	34	..	A. lumbricoides	Fluid; tuberculosis
	10/ 4/45	...	....	16,800	51	18	31	68	Hookworm	
	10/25/45	85	4.4	14,800	25	19	56	26	T. trichiura	
	11/15/45	100	5.2	10,400	31	22	47	23		
IV	9/14/45	...	....	5,200	48	48	4	14	A. lumbricoides	Tuberculosis
	9/21/45	95	....	5,800	59	38	3	15	Hookworm	
	9/25/45	...	....	5,600	46	46	8	6	T. trichiura	
	10/20/45	75	3.7	.....	..	..	..	16		
	11/16/45	85	4.2	6,200	53	44	3	6		
V	2/27/45	...	....	21,900	72	19	9	..	E. nana	Fluid; tuberculosis
	8/30/45	...	....	.....	..	..	..	44	T. trichiura	
	9/19/45	95	4.8	15,800	36	22	42	16	Hookworm	
	11/ 7/45	...	....	9,400	41	38	21			
	11/17/45	...	....	5,900	52	30	18	33		
VI	6/26/45	...	....	9,600	43	46	11	36	A. lumbricoides	
	8/14/45	70	4.3	17,500	58	22	20	8	Hookworm	
	9/22/45	...	....	.....	..	..	..	13	T. trichiura	
	10/19/45	95	4.9	10,400	51	30	19	11		
	11/16/45	90	4.6	9,600						
VII	6/ 2/45	80	4.2	9,400	46	24	30	39	A. lumbricoides	
	7/10/45	...	....	7,900	52	25	23	..	Hookworm	
	9/ 4/45	...	....	9,800	22	40	38	1	T. trichiura	
	10/12/45	...	....	.....	..	..	..	4		
	10/31/45	80	4.2	9,200	32	42	26	8		
VIII	10/ 8/45	80	3.9	8,700	49	32	19	54	Hookworm	
	10/25/45	75	3.8	10,400	40	20	40			
	11/13/45	60	3.4	8,800	44	30	26	46		
IX	9/17/45	80	4.0	15,200	56	28	16	..	A. lumbricoides	Fluid
	10/24/45	...	....	10,800	43	39	18	..	Hookworm	
	11/ 6/45	...	....	.....	..	..	..	36	T. trichiura	
	11/15/45	90	4.7	9,900	28	51	21			
X	6/ 9/45	...	....	15,900	44	30	26	48	A. lumbricoides	Fluid
	6/15/45	100	5.4	21,000	64	21	15	..	S. stercoralis	
	6/30/45	...	....	18,800	67	14	9	..	Hookworm	
	7/13/45	78	....	17,300	61	33	6			
	7/24/45	80	4.4	15,400	65	19	16			
	8/ 7/45	85	4.7	6,700	75	17	8	48		
	9/11/45	...	....	8,400	54	28	18	48		
	10/16/45	100	5.5	8,000	54	34	12	11		
	11/15/45	...	....	.....	..	..	..	7		
XI	7/16/45	80	4.1	12,800	70	30	..	8	Hookworm	
	11/ 1/45	95	5.0	10,500	50	37	13	30	T. trichiura	
XII	9/10/45	70	3.4	15,400	48	20	32	32	Hookworm	Tuberculosis
	10/20/45	75	4.0	14,200	55	27	18	55	E. nana A. lumbricoides	

peribronchial markings in the initial film and ten days later an area of parenchymal infiltration was noted.

The changes seen could be divided roughly into two groups: in one group the involvement was massive and large areas of density were present (Cases III, IV, V, VII, IX and X); in the second group the changes were diffuse and the lesions were small, soft and generally multiple (Cases I, II, VI, XI and XII). The right lung and the lower lobe were more frequently affected than the left lung and the upper lobe. Both lungs were involved in five subjects (Cases I, II, VI, XI and XII). One lobe invasion was seen in only four instances (Cases IV, VII, VIII and IX).

The massive lesions in which the x-ray shadow indicated consolidation, abscess cavity or fluid had no discernible specific characteristics which suggested the presence of paragonimiasis. Frequently small areas of infiltration were present in the upper lobes in these cases resulting in the diagnosis of tuberculosis. In Case III these shadows

TABLE III

SERUM PROTEINS, NON-PROTEIN NITROGEN, FORMOL GEL TEST, DISTILLED WATER TEST, KAHN AND WASSERMANN TESTS IN TWELVE CASES OF PARAGONIMIASIS

Case	Date	Total Protein Gm. %	Albumin Gm. %	Globulin Gm. %	Albumin / Globulin Ratio	N.P.N. mg. %	Formol Gel Test	Distilled Water Test	Kahn Test	Wassermann Test
I	9/11/45	7.8	...	...	...	..	+	+	?	++
	9/19/45	7.4	3.2	4.2	0.8	..	..	..	?	−
	11/16/45	5.8	3.4	2.4	1.6	32	..	.....	−	
II	9/11/45	7.7								
	9/19/45	7.0	3.6	3.4	1.1	..	..	.....	?	−
	10/26/45	6.5	3.7	2.8	1.3	29	−	+	−	
	11/16/45	6.0	3.6	2.4	1.5					
III	10/24/45	7.4	3.0	4.4	.68	..	+	+++	−	
	10/25/45	7.5	3.1	4.4	1.7	42	..	.....	−	
IV	9/21/45	6.3	3.5	2.8	1/3	..	−	++	−	
	9/25/45	5.8	3.4	2.4	1.6					
	10/15/45	6.1	4.0	2.1	1.9					
	11/16/45	6.4	4.2	2.2	1.8					
V	9/13/45	7.5	3.4	4.1	.8	..	..	.....	−	
	9/19/45	7.0	2.8	4.2	.7	..	..	.....	+	−
	11/17/45	5.7	4.1	1.6	2.5	24	−	+	−	
VI	10/19/45	6.5	5.1	1.4	3.6					
	11/17/45	6.5	3.9	2.5	1.6	..	−	−	−	
VII	10/31/45	5.7	3.6	2.1	1.7	..	−	−	−	
VIII	10/12/45	6.9	3.0	3.9	.75	..	−	++	−	
IX	11/7/45	6.7	3.8	2.9	1.2	..	−	++	?	±
	11/12/45	6.9	3.5	3.4	1.0	..	−	−	?	−
X	10/16/45	6.1	5.0	1.1	4.5	35	−	−	−	
XI	10/30/45	7.4	3.9	3.5	1.1	..	−	++	−	
	11/16/45	6.2	3.6	2.6	1.7	..	..	.....	−	
XII	10/20/45	6.1	4.6	1.5	3.1	35	−	−	−	−

preceded the onset of fluid and were associated with the presence of both tubercle bacilli and typical ova; in Case v the shadows followed the appearance of fluid and were also associated with both tubercle bacilli and ova. Within two months after therapy these small areas of involvement were markedly diminished in size in Case III and had entirely disappeared in Case v. A small area of infiltration was seen in two other patients (Cases IX and X) complicated by fluid. In neither case were tubercle bacilli found and in Case X typical ova were repeatedly recovered from the pleural fluid.

The etiology of the x-ray shadows in these cases must remain moot in the absence of pathologic examination and prolonged follow-up. The resolution of the lesions in such short periods under observation, if tuberculous, seemed most unusual. Tubercle bacilli were found only rarely in spite of assiduous search, and the disappearance of ova and decrease of sputum roughly paralleled the clinical and x-ray improvement. The presence of tuberculosis is undeniable in these cases but whether this disease was responsible solely for the x-ray appearance may be questioned. It is more likely that the association of tuberculosis and paragonimiasis contributed to the roentgenologic picture, but the subjective relief and decrease of pulmonary symptoms following emetine suggest that the rôle of the fluke was more important than that of the tubercle bacilli in causing the x-ray changes.

In one patient a large abscess cavity was noted in the right lower lobe. This closed spontaneously, prior to therapy, over a period of five months. Following therapy, this shadow had cleared only slightly in one month.

The lesions (Cases I, II, VI, XI and XII) which are believed strongly suggestive of paragonimiasis may be simulated by the early pulmonary lesions of S. japonica. The pattern seen follows the experimental mode of spread in that the lower lobes of both lungs are involved primarily by small soft areas measuring 1 to 2 cm. in diameter. Larger lesions are encountered close to the diaphragm. In the upper lobes the first and second interspace are rarely involved. At times the shadows assume a patchy distribution in the lateral lung fields. While the general impression is one of mottling, the lesions are larger, less numerous, more discrete and not as dense as those seen in miliary tuberculosis. (Figs. 1 and 2.)

Therapy resulted in the disappearance of the shadows in only case (Case VI). (Figs. 3 and 4.) There was no apparent effect in Cases I, II, XI and XII.

TREATMENT

As the patients were observed for very few months the end results of the treatment are not shown and only the early and immediate effects are available. Tartar emetic (1 per cent) was arbitrarily chosen in the first four cases because it was a drug under constant use in the treatment of schistosomiasis. It was employed in Cases I, II, IV and V and it was badly tolerated. Cough, sputum and chest pain were markedly increased immediately and for some time after injection. There was no dimunition, moreover, in the excretion of ova. Emetine hydrochloride intramuscularly was substituted and continued thereafter in all patients. This drug was well tolerated, reactions were few and when present were minor in nature.

The effect of treatment was assessed by the evaluation of relief of symptoms, the disappearance of ova in the sputum and the resolution of the x-ray shadows.

Symptomatic Relief. Nine of the twelve patients received definite subjective relief in a short period of time. This period followed shortly after the injections of a total dosage of 0.3 to 0.36 Gm. of emetine hydrochloride. Pulmonary symptoms such as chest pain, cough and sputum decreased. Although a sense of well being appeared relatively quickly, there was a lag between the decrease in frequency and severity of the cough and the decrease of sputum.

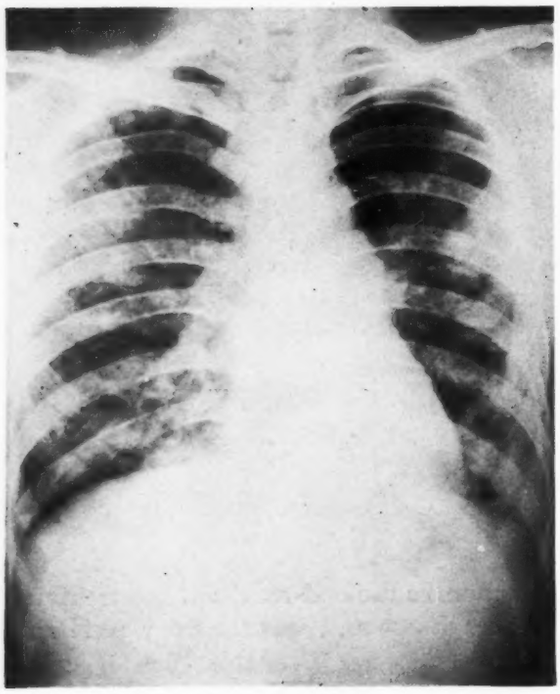

FIG. 1. Characteristic lesions of pulmonary paragonimiasis (Case II, August 26, 1945).

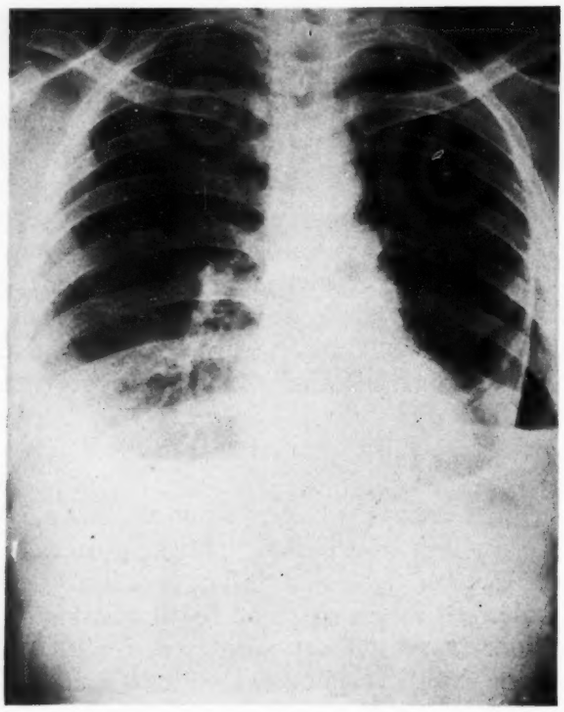

FIG. 2. Pyopneumothorax and empyema illustrating massive lesions in paragonimiasis (Case X, October 14, 1945).

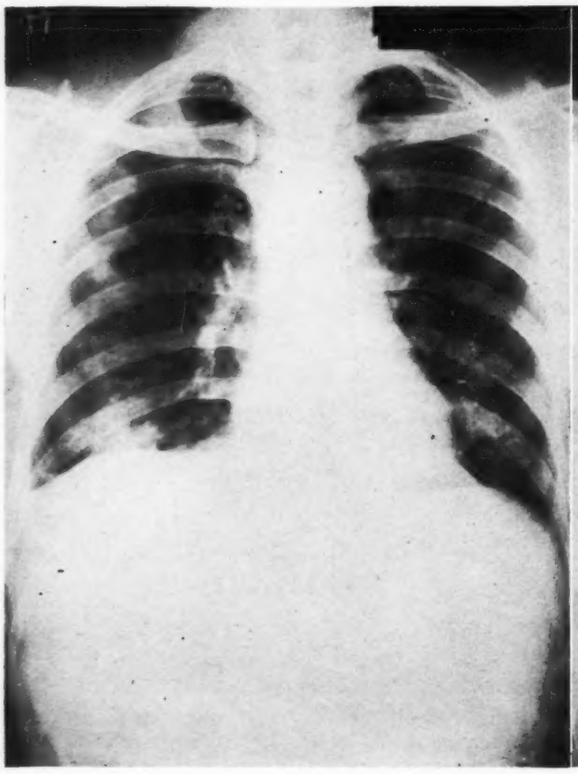

FIG. 3. Film demonstrates increased basal involvement and characteristic mottling prior to therapy (Case VI, August 28, 1945).

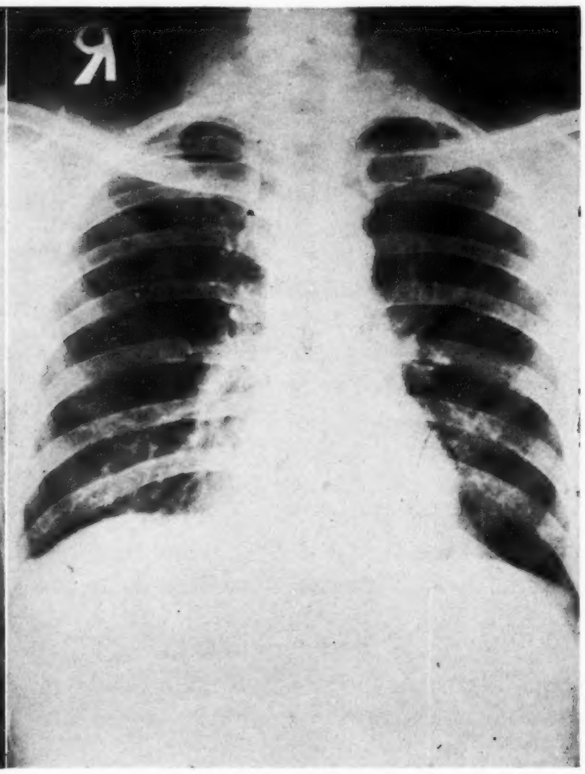

FIG. 4. Film from the same patient showing disappearance of lesions three months later (Case VI, November 15, 1945).

Disappearance of Ova. Experience in the detection of ova in sputum in this disease produces caution in the evaluation of results based upon the disappearance of ova. Negative examination for many days interposed between the demonstration of ova are not uncommon. In these cases ova were discovered in seven of twelve patients, one and thirty days following the first course of treatment. Although in this compilation of cases emetine employed for any indication was considered a course and hence varied in amounts from 0.1 to 0.54 Gm., it would appear significant that ova were found after a dosage of 0.54 Gm. of the drug.

There was no apparent relationship between the duration of symptoms and the effect of emetine on the disappearance of ova as the following table indicates:

Duration of Symptoms (Months)	*Sputum Positive (Case)*	*Sputum Negative after Therapy (Case)*
1–6	VIII	
7–12	II, VII, IX	V
13–18	X	
19–24		VI
25–30	XIII	
31–36	I, XI	XII

All cases are included above as positive in which ova were found after treatment even though in three instances Cases VI (0.48 Gm.), VIII (0.54 Gm.) and XI (0.48 Gm.) the sputum became negative the second day after treatment and apparently remained so thereafter. Following the second course of therapy, the sputum became negative in three cases. In Case X in which the sputum was repeatedly negative three courses were necessary to secure a negative pleural fluid.

The cases in this series are too few to permit determination of the optimum amount of drug required for the disappearance of ova. Ova were found on at least the first day after 0.54 Gm. had been administered and pleural fluid still produced ova after 1.2 Gm. of the drug. In eleven of twelve cases sputum and pleural fluid were negative at the conclusion of the observation period. The one remaining positive case (Case VII) had had only one course of 0.48 Gm. of emetine. In four patients (Cases I, II, IX and X) disappearance of ova persisting after one course was accomplished by repetition of emetine.

X-ray. The shadows demonstrated by x-ray regressed in less than one-half the patients after emetine administration. In only three instances (Cases V, VI and X) was a relatively normal chest film obtained, and in two subjects (Cases III and IX) there were signs of slight to moderate resolution. In the remaining patients there was no evidence of change. Four of the five patients in whom x-ray improvement took place were those in whom fluid had been demonstrated. Only one subject (Case VI) showed resolution of parenchymal involvement. The possibility remains that if a follow-up had been available, the x-ray results might have been better as in only one case was a film taken as long as five months after the first course of emetine. In the remainder the time interval was less than two months.

In summary, tartar emetic was tolerated poorly by four patients and did not appear effective in its brief trial. Emetine hydrochloride resulted in prompt and considerable subjective relief. Its repeated use was followed by the disappearance of ova in the sputum and pleural fluid in one instance. There was only slight effect on the pulmonary parenchymal change within two months following its administration.

DIAGNOSIS

When the pathology of paragonimiasis is recalled, it is apparent that many pulmonary diseases may be simulated. The non-specific symptoms and physical findings of paragonimiasis require that diagnosis be dependent upon recovery of ova. There are, however, features of the disease which aid in its diagnosis and lead to a more intensive search for ova.

The history may indicate exposure in an endemic region or may even disclose the

ingestion of raw, wine-soaked or incompletely cooked fresh-water crabs or crayfish. The minimal systemic reaction, lack of fever, weight loss, sweats and asthenia, is striking on physical examination. The relative well being of the patient seems incongruous when it is contrasted with the type and duration of the symptoms. Although all our patients presented some physical findings in the lungs, these were minimal when consideration was given to the pathologic involvement noted by x-ray and the presence of hemoptysis of long duration. Others have cited the paucity of physical signs in this disease. X-ray of the chest is most helpful in diagnosis. Bizarre multiple lesions such as have been described should focus attention upon the possibility of a parasitic infection, and normal lung x-rays in the presence of hemoptysis and a history of sojourn in an endemic region should direct attention to the possibility of paragonimiasis. Suspicion of the disease is the important thing and a search of unstained sputum for ova should be made in every instance in which exposure is established and protracted cough exists.

CASE REPORTS

CASE I. A twenty-nine year old Filipino male was admitted August 27, 1945, complaining of cough, intermittent hemoptysis and pain in the chest of two years' duration.

Following a recurrence of malaria in February, 1943, he noted pain in the right chest and hemoptysis. During the next two and one-half years he lost 20 pounds, became weak and tired and developed a constant cough productive of blood-streaked sputum. He had always eaten raw shrimp, crab and crayfish, and continued this practice in the mountainous regions of Mindanao as a guerrilla. Other than malaria in 1942 he denied all illnesses. There was no family history of pulmonary tuberculosis.

On admission to a hospital on June 22, 1945, bilateral apical râles were noted. X-ray examination showed several areas of soft and fibrous infiltration in the right upper and middle lung fields with suggestion of cavitation in several areas. Sputum was negative for tubercle bacilli. There was no fever during the remainder of his two-month stay and he was eventually transferred to this hospital.

Physical examination revealed a Filipino male not acutely ill; temperature 98.6°F.; pulse 68; respirations 18, weight 120 pounds; blood pressure 100/80. There were numerous crepitant râles at the right apex and the inner midscapula region. A leukocyte count was 8,800 per cu.mm. with 54 per cent neutrophils, 14 per cent lymphocytes and 32 per cent eosinophils. The sedimentation rate was 36 mm. in one hour. A smear for malarial parasites was negative. The sputum was negative on four occasions for tubercle bacilli but contained ova of P. westermani repeatedly. The stool contained ova of A. lumbricoides, hookworm and P. westermani. Urinalysis was negative. The Kahn test was doubtful, and the Wassermann was two plus on September 11th and negative on September 25th.

Treatment with tartar emetic (2 per cent solution) was started on September 10th and was discontinued September 27th after 39 cc. had been given because of severe reaction and apparent lack of beneficial effect. Emetine hydrochloride (0.06 Gm. daily) was begun September 29th and continued for six days.

About one week following the combined treatment it was noted that 10 pounds loss of weight had occurred, chest pain had cleared, cough was less and afternoon fever had appeared, ranging between 99° and 100°F. This continued for three weeks until October 31st. Occasional blood-streaked, mucopurulent sputum still contained ova two weeks following emetine. In the next week the weight increased 2 pounds and the cough and sputum had strikingly decreased to less than 12 cc. daily. There was no roentgenologic change. Schistosomiasis was detected proctoscopically about this time but it was determined to re-treat the paragonimiasis. On October 31st another course of emetine (0.06 Gm. daily) was begun and continued for eight days. About one week later although there was a weight gain of 4 pounds, the cough and chest pain were still present occasionally. The following week there was further subjective improvement, the symptoms were minimal and the sputum had decreased to such degree that it was difficult to obtain a specimen for examination. An x-ray of the lung on November 16th showed no change.

CASE II. A twenty-five year old Filipino male was transferred to this hospital on Au-

gust 26, 1945, with a diagnosis of pulmonary paragonimiasis.

The history of his present illness dated back to February, 1945, when he developed a cough productive of brownish-colored sputum containing specks of blood the size of rice grains. He was hospitalized March 2, 1945, because of hemoptysis. He had been in good health and denied all illnesses except intestinal parasite infestation as a child. Born in Leyte, P.I. he was very fond of raw crayfish, crabs and shrimps which had frequently been his only source of food as a guerrilla. There was no family history of tuberculosis. During hospitalization he had been afebrile; examination had shown medium râles at the left base and fine crepitant râles at the right apex. An x-ray of the chest on March 20, 1945, showed hard and soft irregular mottled densities through both lung fields. Several areas were considered suggestive of cavitation. No change was noted by x-ray on four occasions in the next six months and cavitation was not substantiated. The sputum contained ova of P. westermani on April 9th; tubercle bacilli were not found on three examinations. The hemoglobin was 75 per cent, erythrocytes 4,800,000 per cu. mm., leukocytes 8,000 per cu. mm. with 62 per cent neutrophils and 38 per cent lymphocytes. Urinalysis was negative. Ova of A. lumbricoides were present in the stool. No specific treatment was given other than hexylresorcinol for the ascariasis.

On admission he weighed 138 pounds and did not appear ill. His general appearance was in striking contrast with the findings in the x-rays of his chest. There were medium râles at the axilla and the left base. There was a short apical systolic blow which was transmitted; blood pressure 115/60; the spleen was firm and easily felt one finger's breadth below the costal margin.

A smear for malarial parasites was negative. A sedimentation rate was 20 mm. per hour. A Kahn test gave a doubtful and a Wassermann test a negative result. Stools contained ova of hookworm, A. lumbricoides, P. westermani and cysts of E. histolytica. Sputum contained ova of P. westermani on September 7th to 14th.

Tartar emetic therapy (2 per cent) was begun on September 14th. His cough continued, intensified in the early morning hours, productive daily of 30 to 60 cc. of tenacious, brownish-streaked sputum containing shreds of blood resembling tobacco flakes. After eight doses of tartar emetic solution had been given it was discontinued on September 28th. Throughout its administration sporadic sputum examination showed the presence of ova. Following tartar emetic on September 29th, emetine hydrochloride (0.06 Gm.) was given daily for six days. Unfortunately the sputum was not examined during this time. However, it was quite definitely established that ova were still being produced several days after the conclusion of treatment. Subjectively there was striking improvement within one week. On October 10th there were no complaints, cough was infrequent, occasionally productive of mucoid material. His weight was 135 pounds, examination disclosed diminished breath sounds and occasional moist râles at the left base. The liver was palpable three fingers' breadth below the costal margin. Ten days later an unexplained fever reaching 102°F. was present for two days. Sputum not exceeding 8 cc. daily was found to contain ova. The following week the sputum increased to 16 cc. daily although he remained afebrile, and another course of emetine (0.06 Gm.) was started October 31st and completed November 8th. At this time he was asymptomatic except for an occasional cough productive of 4 to 8 cc. of sputum daily. X-rays of the chest October 22nd and November 16th showed no change in the appearance of the mottled infiltration extending throughout both lung fields. The sputum was negative for tubercle bacilli on eleven occasions.

Case III. A twenty-eight year old Filipino male was admitted to another hospital on September 11, 1945, where a detailed history was not obtained. Apparently the only finding of note on admission was a yellow patch on the right tonsil. One week later he had chills, cough, profuse sweats and signs of consolidation in the right lower lobe; his temperature ranged from 99.4° to 103°F. An x-ray at this time revealed irregularly dense infiltration in the left lung. Sputum on five occasions was negative for tubercle bacilli. The leukocyte count was 14,600 per cu. mm. with 49 per cent neutrophils, 16 per cent lymphocytes and 34 per cent eosinophils. The stool contained ova of A. lumbricoides and hookworm. A stool culture was negative for pathogens. Urinalysis was negative. Penicillin (20,000 units every three hours) was given for nine days without noticeable effect.

He was admitted on September 25, 1945.

His illness was found to date back to August, 1943, when he developed chills diagnosed clinically as malaria. Recovery was slow and asthenia was especially prominent. An intermittent cough began one month later together with dyspnea on exertion and pain in the left chest increased by respiratory motion. Palpitation, gastric distress, frequent vomiting and weight loss followed. He was admitted to a guerrilla hospital where he stayed for ten months. His cough became especially severe at night but was present only occasionally during the day. Sputum averaged about one cupful daily. He was unable to carry out his duties following hospitalization and remained in his quarters in the mountains until his admission to a U. S. Army hospital in September, 1945. He had been a guerrilla in Cebu, P.I. since the Japanese occupation. He liked seafood and as a guerrilla had frequently existed on raw and semi-cooked crabs and crayfish. He denied all previous illnesses except two attacks of malaria, neither verified by smear. One uncle, a close contact, had tuberculosis but the remainder of the family was in good health. His usual weight was 121 pounds.

On physical examination he no longer appeared acutely ill, his weight was 143 pounds, temperature 98.6°F.; blood pressure 92/60. There was a friction rub with signs of moderate pleural effusion at the left base; the liver was palpable three fingers below the costal margin; the spleen was not felt. A leukocyte count was 16,800 per cu. mm. with 51 per cent neutrophils, 18 per cent lymphocytes and 31 per cent eosinophils. Two smears were negative for malarial parasites. Sputum was negative for tubercle bacilli and ova. On October 6th although the sputum was still negative for tubercle bacilli, it contained ova of P. westermani. These were demonstrated repeatedly thereafter. X-ray of the chest on October 5th showed a homogeneous density at the left base which extended up the lateral portion of the chest to the second anterior rib; there was a mottled infiltration in the right apex and in the lower portion of the right upper lobe. Thoracentesis on October 13th yielded 50 cc. of blood-tinged fluid from the left chest; this was negative for organisms on smear and culture and did not contain ova. His condition remained stationary. There was no fever. The sputum, a thin but tenacious fluid occasionally containing dark bloody flecks, measured 60 to 80 cc. daily.

Emetine hydrochloride (0.04 Gm.) was given daily from October 18th to October 29th without reaction. During therapy the sputum on three occasions did not contain ova but the day following the conclusion of therapy, October 30th, ova were present. Tubercle bacilli were found on two occasions, October 29th and November 10th.

Following emetine there was subjective improvement. He stated that he was stronger and the cough, although still present, was definitely less severe and was not increased nocturnally. The sputum had decreased gradually and no longer contained bloody flecks, but was still purulent and excessive in amount three weeks later. He had gained 3 pounds. The physical signs of either fluid or markedly thickened pleura were still present at the left base. X-ray of the chest at this time, November 20th, showed marked pleural thickening at both bases, the left more extensive; in addition there was hazy, streaked infiltration in the medial portion of both bases. The patchy infiltration involving the right upper lobe had resolved considerably.

Case IV. A thirty year old Filipino male was hospitalized at another institution August 30, 1945, complaining of fever, chest pain and cough of one week's duration. Except for one attack of malaria some years before, he had been well until one week before admission when he felt "feverish" for two days. He then noted a frequent cough productive of a yellow, thin mucopurulent sputum containing rice-sized specks of blood, with the simultaneous appearance of sharp, transient chest pain unaffected by respiration.

He was born on Negros, P.I. and had been a guerrilla there living in the mountains. He was fond of fish and shellfish, both cooked and raw. His usual weight was 115 pounds. There was no family history of tuberculosis.

Physical examination disclosed moist râles at the left base and a palpable spleen edge. An x-ray of the chest showed a soft, mottled infiltration in the left first anterior interspace. He was transferred to this hospital the next day.

On admission the findings were confirmed. He was afebrile. A leukocyte count was 5,200 per cu. mm. with 48 per cent neutrophils, 48 per cent lymphocytes and 4 per cent eosinophils. A sedimentation rate was 14 mm. per one hour. Stools contained ova of A. lumbricoides, hookworm and T. trichiura. Sputum on September 13th was found to contain one ovum of P.

westermani. Repeated daily sputum was negative thereafter until eight days later on September 21st. A tuberculin test (P.P.D.) was negative with the first dilution and weakly positive with the second. Sputum was negative for tubercle bacilli on three examinations.

There was no change in the general condition in the next three weeks; frequent cough with bloody expectoration continued in amounts varying from 30 to 60 cc. daily. On September 19th tartar emetic (2 per cent was given but discontinued after seven doses (41.5 cc.) because it was tolerated poorly and there was increase of cough. On October 29th emetine hydrochloride (0.06 Gm. daily) was started and completed November 5th. One day after onset of emetine therapy many tubercle bacilli were found in the sputum.

One week following the conclusion of emetine therapy there was definite improvement. The weight had increased 5 pounds, the cough was less frequent and chest pain had disappeared. Sputum had also decreased in amount but this was more clearly manifest at the end of another week; daily amounts varied from 4 to 20 cc. consisting principally of a thin watery fluid. Twelve sputum examinations (six concentrated) were negative thereafter for ova and tubercle bacilli.

Three weeks after completion of emetine therapy the patient was asymptomatic and his weight was 124 pounds. There was no change in the x-ray appearance of the chest from September 16th to November 16th.

Case v. A nineteen year old Filipino male was admitted to an evacuation hospital February 26, 1945, complaining of cough and dyspnea. His present illness began in December, 1944, with loss of appetite, cough and weakness. These symptoms continued and gradually chest pain, aggravated by respiration, chilly sensations and dyspnea appeared. On the day of admission he became "very sick."

He had been a student prior to the invasion and joining the guerrillas he lived in the mountains of Leyte where he ate both raw and cooked crabs, crayfish and mud fish (alimongo and haloan). There was no family history of tuberculosis.

Physical examination showed a bilateral hydropneumothorax. The leukocyte count was 21,800 per cu. mm. with 72 per cent neutrophils, 19 per cent lymphocytes and 9 per cent eosinophils. Fifteen hundred cc. of greyish-green purulent fluid was withdrawn from both right and left pleural cavities. The fluid was sterile after forty-eight hours and there were no organisms seen on smear. A sputum specimen contained tubercle bacilli. During the remainder of the observation fourteen subsequent specimens, six by concentrated technics, were negative. He was transferred and on March 7th another thoracentesis was done because of respiratory embarrassment, 500 cc. of greyish-yellow cloudy fluid containing mucopurulent particles being withdrawn from the right chest. This, too, proved sterile and a search for bacteria and parasites was negative. One week later thoracentesis was again necessary but only 200 cc. of greyish-yellow caseous material was withdrawn. Two weeks later, June 4th, 500 cc. of thick green purulent fluid was again aspirated and 75,000 units of penicillin were instilled. His condition thereafter improved, he became afebrile and was transferred here August 25, 1945.

Physical examination showed a thin young male, weight 118 pounds (normal 128 pounds), who appeared chronically ill. There were râles, dullness and diminished to absent breath sounds over both lower lobes. X-ray of the chest showed a hazy infiltration above the third rib anterior on the right. There was increased bronchovascular markings in each lung and pleural thickening along both lateral chest walls more marked at the bases. The hemoglobin was 95 per cent (Sahli) the erythrocyte count was 4,800,000 per cu. mm. leukocytes 15,800 per cu. mm. with 36 per cent neutrophils, 22 per cent lymphocytes and 42 per cent eosinophils. On September 10th a few ova of P. westermani were seen in the sputum but daily specimens for the next week were negative. On September 22nd ova of P. westermani were identified in the stool, in addition to ova of T. trichiura, hookworm and cysts of E. nana. The next day ova of P. westermani were found in the sputum. Tartar emetic therapy (2 per cent) was begun on September 10th but discontinued on September 26th (total of 54 cc.) because of reaction and apparent lack of response to the drug. On September 29th emetine hydrochloride (0.06 Gm. daily) was started. It was completed October 4th.

One week following conclusion of therapy his weight was 120 pounds, cough had decreased and mucopurulent sputum without trace of blood was present in lesser amounts. The patient

stated that although following thoracentesis he felt much better he thought that all his symptoms had been decreased following the taking of emetine. October 22nd, two and one-half weeks after emetine, an x-ray showed considerable resolution of the pulmonary infiltration in the first three interspaces on the right. On November 6th his weight was 128 pounds, cough was minimal and he was asymptomatic. One week later, November 13th, he was still asymptomatic; the temperature varied from 99° to 99.4°F., the sedimentation rate had risen to 33 mm. per hour and the quantity of sputum varied from 0 to 6 cc. daily. The x-ray of the chest showed no change in the basal pleural thickening and the infiltration in the right lung had completely resolved. Further sputum examinations were negative for ova.

CASE VI. A twenty-eight year old Filipino male was transferred to this hospital on August 25, 1945, from another institution where he had been hospitalized for two months.

His illness dated back to February, 1944, when he developed fever, chills and hemoptysis. He continued as a guerrilla in spite of these symptoms. Fever and chills disappeared in a few days but cough continued and became excessive at night, resulting in insomnia and loss of weight. Chest pain, aggravated by respiratory movement, appeared. The persistence of hemoptysis, recurrence of pain and constant fatigue finally made him seek medical attention in June, 1945. As a guerrilla he had eaten both raw and cooked fresh-water eel (casili), shrimp (ulang) and crab (alimongo). There was no family history of tuberculosis.

On examination June 22nd the temperature was 98.6°F. and râles and increased vocal fremitus were noted at the left apex. The sedimentation rate was 36 mm. per hour; the leukocyte count was 4,600 per cu. mm. with 43 per cent neutrophils, 46 per cent lymphocytes and 11 per cent eosinophils. An x-ray of the chest showed minimal infiltration with bronchial distribution in the left lower lung field which was interpreted as minimal pneumonitis. Sputum was negative for tubercle bacilli. His condition remained unchanged for the next two months. Cough and hemoptysis continued, the temperature remained normal (99.8° to 100°F. for only four days) and he was eventually transferred.

Physical examination on August 26, 1945, showed a well developed and nourished male, weight 126 pounds (normal 138 pounds), temperature 98.8°F., pulse 80, respirations 20. There were a few scattered râles at both apices and increased vocal fremitus at the right base. An x-ray of the chest on August 28th revealed areas of patchy infiltration along the lateral portion of the right lung, more marked at the base; the left upper lobe was similarly involved and there was pleural thickening in both costophrenic sinuses. The x-rays were considered compatible with a diagnosis of paragonimiasis and a search for ova began. The sputum was negative previously on two occasions for tubercle bacilli. On October 16th sputum by concentration technic was negative for tubercle bacilli but contained ova of P. westermani. These findings were repeated the following day. On October 18th emetine hydrochloride (0.06 Gm. daily) therapy was started and completed October 26th. Following the fifth dose of emetine his condition was definitely improved. Cough lessened, pain and dyspnea disappeared, and sputum was markedly decreased in amount and altered in character from a blood-specked mucopurulent fluid to a thin watery saliva. Because of a leukocyte count of 10,400 with 51 per cent eosinophils he was proctoscoped. This procedure was entirely negative. Stools contained ova of A. lumbricoides, hookworm and T. trichiura. On November 18th his weight was 124 pounds; three weeks following the treatment with emetine he was asymptomatic. His daily measured sputum, principally saliva, did not exceed 8 cc. His last x-ray on November 16, 1945, showed clear lung fields.

CASE VII. A twenty-three year old Filipino guerrilla was first admitted to a field hospital June 1, 1945, because of hemoptysis. His illness began November, 1944, when he noted the onset of a nocturnal cough productive of very little sputum. One month later anterior chest pain, brought on by exertion, appeared and shortly afterward hemoptysis began which continued for a month. Hematemesis on two or three occasions, night sweats and slight loss of weight were also present. Shortly after the Japanese invasion he had become a guerrilla and living in the mountains had eaten both raw and boiled fresh-water crayfish. There was no family history of tuberculosis.

Examination revealed evidences of slight loss of weight, weight 133 pounds, temperature 98.6°F., pulse 68, respirations 18 and blood pressure 100/64. There were moist râles and

diminished breath sounds in the right, middle and lower lobes.

An x-ray of the chest revealed multiple cavitation in the right lower lobe, surrounded by a large area of increased density. Hemoglobin was 80 per cent (Sahli) the erythrocyte count was 4,200,000 per cu. mm; the leukocyte count was 9,400 per cu. mm. with 45 per cent neutrophils, 24 per cent lymphocytes, 30 per cent eosinophils and 1 per cent monocytes. The sputum was negative for tubercle bacilli. The sedimentation rate was 39 mm. in one hour. Urinalysis was negative. Stool examination revealed ova of A. lumbricoides, T. trichiura and hookworm.

His condition remained unchanged in the next two and one-half months; the cough continued unabated and there was no loss of weight. He was afebrile except for a malarial episode at which time a blood smear revealed Pl. vivax. There was little change roentgenologically, the areas of cavitation were less distinct and the surrounding density was slightly increased.

On transfer to this hospital, August 28, 1945, the previously noted findings were confirmed. Proctoscopic examination revealed ulceration between the first and second folds although nine stool examinations were negative for amebae. A thoracentesis of the right chest yielded 5 cc. of sterile bloody fluid which did not contain ova or parasites. In view of the great likelihood that E. histolytica infection was present a course of emetine hydrochloride (0.06 Gm. daily) was given for eight days and completed September 28, 1945. There was no immediate effect but a gradual diminution of the cough and decrease in sputum were apparent. The sputum, however, remained purulent and it was still occasionally bloody one month later. The chest pain gradually disappeared and a weight gain of 7 pounds occurred. Tubercle bacilli were not present on nine sputum examinations. On October 29th, after four negative examinations, ova of P. westermani were found; eleven subsequent examinations were negative. Repeated x-ray examinations and fluourscopy from June to November showed the spontaneous closure and disappearance of two cavities in the right middle lobe and the appearance and disappearance of a large cavity in the right lower lobe. On the final film November 17, 1945, there was moderate clearing of the surrounding density in the right middle and lower lobe.

CASE VIII. A thirty-nine year old Filipino male was admitted October 6, 1945, complaining of fever, cough, hemoptysis and dull pain in the left calf and thigh. His illness dated back to July, 1945, when he developed chills and fever which was diagnosed clinically as malaria. He made a gradual recovery from this illness until August 15th when he began to spit blood like grains of rice. He became feverish but kept on working. The cough became constant and was especially marked in the evening and early morning. Following the onset of cough he noticed the appearance of anterior chest pain and an ache in the left calf and thigh. There was no malaise or weakness and he stated that if not for the cough he would feel well. He had lived in Mindanoa and had been a Japanese prisoner until January 20, 1943. He frequently ate shellfish and fresh-water crabs (alimongo), both raw and cooked, but insisted that he had eaten none since May, 1942. His previous health was excellent. There was no family history of pulmonary tuberculosis.

Examination revealed a well developed male, temperature 98.6°F., pulse 72, respirations 18, blood pressure 106/66 and weight 118 pounds. There were medium moist râles at the right apex and scattered moist râles at both bases. The extremities were normal. Hemoglobin was 80 per cent, erythrocyte count 3,900,000 per cu. mm., the leukocyte count was 8,200 per cu. mm. with 49 per cent neutrophils, 32 per cent lymphocytes and 19 per cent eosinophils. The sedimentation rate was 54 mm. in one hour. The sputum was purulent and contained dark blood; tubercle bacilli were not present and many ova of P. westermani were seen. An x-ray of the chest showed striking accentuation of the peribronchial markings. Ten days later a new soft mottled area was present in the right first anterior interspace and a similar area was questionably present in the left mid-lung field. Emetine hydrochloride (0.06 Gm. daily) was given from November 5th to November 13th. During the short period of five weeks' observation there was no fever and the patient subjectively felt well. The cough was troublesome and productive of bloody, purulent sputum measuring 60 cc. daily. There was mild diffuse, shifting chest pain. The physical findings did not change. One week after emetine, although there was little objective change, the patient stated that he was better and his weight had increased to 122 pounds. There was no change in the chest pain, cough or amount of sputum. Ova were obtained on two occasions in the

sputum and stool during therapy and one day following. Two specimens were negative one week later. Eleven specimens, four by concentration technics, were negative for tubercle bacilli. An x-ray of the chest was unchanged one week following therapy.

CASE IX. A twenty year old Filipino male was admitted October 10, 1945, with a diagnosis of pleurisy with effusion.

His present illness began one year before with a constant nonproductive cough. Four months later he noted the appearance of small flecks of blood. In the next two months he developed marked weakness and anterior chest pain aggravated by respiratory movement. These symptoms continued unabated for three months when he developed fever, chills and dyspnea and was hospitalized at a guerrilla installation for one month. He lived in Mindanoa, P.I. and had served as a guerrilla in the mountains of that island. He frequently ate fresh-water fish and shell-fish (alimongo, haloan and pasayan). He had been well except for five recurrences of malaria. There was no family history of tuberculosis.

He stayed in the guerrilla hospital for a month and was then transferred to an army hospital where he was found to have a right pyothorax. Four hundred cc. of thick creamy sterile fluid was withdrawn from the right chest September 20th. A centrifuged specimen of this fluid was negative for ova and parasitic cysts. Emetine hydrochloride (0.06 Gm. daily) was given for three doses in combination with penicillin, 25,000 units every four hours. There was no note on the chart to explain this treatment; presumably the pyothorax was thought to result from either paragonimiasis or amebic liver abscess. By September 30th he was much more comfortable, the chest pain had cleared, and the dyspnea was diminished although the physical signs were apparently unchanged. X-ray examination showed diminution of the fluid.

On admission he did not appear acutely ill. The physical signs of thickened pleura with fluid were evident. The hemoglobin content of the blood was 90 per cent, the erythrocyte count was 4,700,000 per cu. mm., the leukocyte count was 10,800 with 43 per cent neutrophils, 39 per cent lymphocytes and 18 per cent, eosinophils. The sputum contained ova of P. westermani on four different days and was negative thereafter on ten occasions. The urinalysis was negative. The Kahn test on two occasions gave a doubtful reaction and the Wassermann test was negative. The stool contained ova of A. lumbricoides, hookworm and T. trichiura.

Eight cc. of chocolate-red purulent fluid, containing yellowish curd-like material, was withdrawn from the right chest on November 7th. Microscopically this was composed of leukocytes in various stages of degeneration, red cells, epithelial cells and yeast forms; eosinophils were rare and ova of P. westermani were not seen. Treatment with emetine hydrochloride (0.04 Gm. daily) was started November 7th and completed November 18th.

During therapy his appetite decreased and he lost 5½ pounds of weight. This was regained within four days, at the conclusion of treatment. Near the end of therapy, November 15th, physical and x-ray examination showed no change. Following therapy he felt slightly better. The cough was less and there was striking diminution of sputum. Ova were not obtained by concentration technic in five specimens.

One week post-therapy, November 25th, the cough was non-productive and less frequent, chest pain and dyspnea were gone, and it was noted that hemoptysis had been absent for over two weeks. The signs of thickened pleura and fluid were still persistent.

CASE X. A twenty-seven year old Filipino male was admitted to this hospital with a diagnosis of paragonimiasis on October 10, 1945.

He had been hospitalized in several institutions since June 9, 1945. As a guerrilla in the mountains of Mindanoa he had eaten fresh-water crabs, raw and semi-cooked, in June, 1944. There was no family history of pulmonary tuberculosis. About September, 1944, he noted the onset of non-productive cough. This persisted, and early in February, 1945, dyspnea, anterior chest pain and speckled bloody sputum appeared and gradully increased in severity. In June hemoptysis prompted him to enter a hospital.

On admission he was acutely ill, dyspneic, coughing frequently but afebrile. He had signs of bilateral effusion. The hemoglobin content of the blood was 100 per cent (Sahli), erythrocyte count was 5,400,000 per cu. mm., the leukocyte count was 21,000 with 64 per cent neutrophils, 21 per cent lymphocytes and 15 per cent eosinophils. Multiple thoracentesis in the course of several days yielded 2,500 cc. from the right and 2,000 cc. from the left pleural cavity, an

opalescent yellow fluid containing yellow flaky material. Ova of P. westermani were found in the fluid repeatedly. He was given a course of emetine hydrochloride, total dosage 0.66 Gm. from June 12th to June 22nd, and on June 25th emetine 0.03 Gm. was injected into each pleural cavity. Between July 13th and the 21st he received 0.54 Gm. of this drug again, intramuscularly, and on July 4th 0.04 Gm. was instilled into each pleural cavity following thoracentesis. On July 21st the fluid was less in amount and clearer, which led to the belief that loculation was present. Ova were still noted in the pleural fluid bilaterally but were infrequent and required a more diligent search for demonstration. The sputum had decreased from 120 cc. to 15 cc. daily. It contained ova only in one specimen (June 25th) and was negative on five occasions. The general improvement was definite.

He was transferred to still another hospital September 9th and at this institution signs of a moderate amount of fluid were still present. A leukocyte count was 8,400 per cu. mm. with 54 per cent neutrophils, 28 per cent lymphocytes and 18 per cent eosinophils. The sputum was negative for tubercle bacilli and ova. On September 17th, 600 cc. of cream-colored, thick fluid containing ova was obtained from the right chest. During this period weakness, anorexia and anterior chest pain were prominent. Another course of emetine was given (0.06 Gm.) between September 19th and September 27th. His last thoracentesis was done September 30th and 200 cc. of fluid, identical with that removed September 17th, was obtained from the left chest. It, too, contained ova of P. westermani. Following this procedure there was steady, gradual and consistent improvement. His complaints disappeared and the physical signs diminished. On arrival at this hospital he had evidence only of thickened pleura at the right base. Sputum was obtained with difficulty for examination. A total of eleven examinations (seven concentrated) were negative for tubercle bacilli. Ten additional examinations were negative for ova of P. westermani. The urinalysis was negative. The sedimentation rate was 11 mm. in one hour. The Kahn test was negative. The stool contained ova of A. lumbricoides, S. stercolis and hookworm. An x-ray of the chest, November 15th, showed bilateral pleural thickening at the base. There was no evidence of pulmonary infiltration. There were no complaints throughout his hospital stay in October and November.

Case xi. A twenty-eight year old Filipino male was transferred from another hospital October 9, 1945, with a diagnosis of pulmonary tuberculosis.

His illness had started in January, 1943, with a constant cough productive of thick, yellow sputum. The cough continued for a year during which time he lost some weight. He then noted chest pain only with cough, dyspnea on exertion and easy fatiguability. In April, 1945, following severe cough, he vomited about a small cupful of blood; since then his cough was constantly productive of rice grain specks of blood.

He had been a guerrilla in Mindanoa. He denied the intake of fresh-water shellfish or fish and insisted he had eaten only sea food. There was no family history of tuberculosis. Physical examination at the previous hospital, July 13, 1945, revealed that he was well developed and well nourished and did not appear ill. There were fine inconstant râles in both lower lobes and increase of spoken voice in the left upper lobe. A chest x-ray the following day showed extensive pulmonary infiltration at the level of the first, second and third anterior interspaces on the right, and at the second and third interspaces on the left. As a result of the x-ray report extensive sputum examinations were done but twenty-three specimens were negative for tubercle bacilli. During his hospital stay the temperature, normal for several weeks at a time, would rise to 101° and 102°F. for two or three days. He felt well, his appetite was good and the cough was moderate with little expectoration.

At this hospital, October 15, 1945, physical examination disclosed medium moist râles at both apices and the left base. His weight was 114 pounds (normal weight was 118 pounds). After one negative sputum examination on October 29th ova of P. westermani were recovered and this was verified on five other occasions in the next two weeks. Eleven specimens, six by concentration, were negative for tubercle bacilli. The hemoglobin of the blood was 95 per cent (Sahli) erythrocytes 5,000,000 per cu. mm., the leukocyte count was 10,500 with 48 per cent neutrophils, 37 per cent lymphocytes and 13 per cent eosinophils. A sedimentation rate was 30 mm. per hour. Stools contained ova of hookworm and T. trichiura. The urinalysis was negative.

In the next few weeks his cough continued

unabated. The chest pain which was not affected by respiratory movement was mild and bilateral and principally confined to the anterior chest. The sputum was greenish-yellow, thin and purulent, reaching 90 cc. daily and rarely contained bloody tobacco-like shreds. During emetine hydrochloride administration (0.06 Gm. daily) from November 6th to 13th, the cough diminished and the pain lessened. The sputum disappeared and only saliva was obtained; however, ova were present for one day after the conclusion of therapy. On November 21st there was no change in the physical signs or x-ray appearance of the lung.

Case xii. A thirty-four year old Filipino male was admitted October 9, 1946, with a diagnosis of paragonimiasis and pulmonary tuberculosis. His present illness dated back to December, 1942, when, following malaria, he developed a cough, bilateral chest pain aggravated by respiratory motion, dyspnea and weakness. Although he lived in Leyte, P.I., he had joined the guerrillas in Mindanoa in August, 1943. He liked shellfish and fish and had eaten them in quantity, both raw and cooked, prior to his illness. As a guerrilla he ate freshwater crab (alimango), mudfish (haloan) shrimp (ulang). There was no family history of tuberculosis. Shortly after becoming a guerrilla his symptoms became more severe and vomiting occurred in the morning. His cough became productive, night sweats appeared and loss of weight and asthenia resulted. He was in and out of hospitals for the next two years. In January, 1945, he spit up blood and hemoptysis had recurred intermittently since then.

Notes were not available until he was admitted to a hospital, August 29, 1945, where it was stated that he was in his seventh month of hospitalization. Examination disclosed soft, bubbling râles throughout both lungs. An x-ray of the chest was interpreted as indicative of far advanced tuberculosis with cavitation. He was transferred to another hospital one week later where it was noted that his temperature was 98.6°F. and that he did not appear ill. Physical examination of the chest showed many fine râles throughout both lung fields together with marked diminution of breath sounds. A leukocyte count was 15,400 per cu. mm. with 48 per cent neutrophils, 20 per cent lymphocytes and 32 per cent eosinophils. Ova of P. westermani were found frequently in the sputum. On one occasion, September 29, 1945, a few acid-fast bacilli were seen. Thereafter a total of twenty-four specimens were examined from September 9th to October 6th, and five specimens by concentration technics were examined from October 19th to November 12th but tubercle bacilli were not found again. A chest x-ray was similarly interpreted as indicative of far advanced tuberculosis with cavitation. He was placed on emetine hydrochloride (0.06 Gm. daily) October 4th for six days and transferred to this hospital.

On admission he complained of bilateral chest pain, cough and dyspnea. The findings of the physical examination were confirmed. The sputum was yellowish-white, purulent and streaked with minute bloody shreds. The hemoglobin content of the blood was 75 per cent and the erythrocyte count was 3,900,000 per cu. mm. The sedimentation rate was 55 mm. in one hour. Urinalysis and Kahn test were negative. The stool contained ova of A. lumbricoides, hookworm and cysts of E. nana. His condition remained unchanged until October 17th when his temperature rose suddenly to 101°F. simultaneously with increase of cough, chest pain and respiratory rate. Physical examination did not explain this episode but sulfadiazine therapy resulted in a normal temperature within two days. Emetine hydrochloride (0.06 Gm. daily) was started the night of October 19th and continued until October 26th. One week later the cough was much improved. There was only occasional left-sided pain, the dyspnea was moderate and medium moist râles were scattered throughout both lungs. His weight, 135 pounds, was only 5 pounds under normal. A tuberculin test (P.P.D.) was negative in the first strength and weakly positive in the second. In the next three weeks his course seemed one of very slow but steady improvement. On November 20th he was afebrile, hemoptysis had been absent for a month although the cough was still severe and productive of about 12 cc. of yellow purulent sputum daily. Chest pain was still present and he appeared ill. The x-ray findings of the chest were unchanged.

SUMMARY

1. Paragonimiasis was encountered in the Philippine Islands among guerrillas hospitalized for observation of tuberculosis.

Twelve cases were found among approximately 250 patients.

2. Coexistent tuberculosis and paragonimiasis were established in four of the twelve cases reported.

3. Paragonimiasis may simulate tuberculosis closely so that the former should be considered in the differential diagnosis of hemoptysis in personnel who have been in endemic regions.

4. Emetine hydrochloride relieved subjective symptoms of paragonimiasis promptly but it had only a slight effect on the pulmonary disorder as indicated by x-ray findings in the period of our observations.

5. Paragonimiasis may produce serum protein changes and transiently positive serologic tests for syphilis.

6. Treatment of this disease is still far from satisfactory and more efficient therapeutic agents are required.

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Studies on Patients with Cirrhosis of the Liver*

Plasma and Liver Lipid Distribution and Its Relation to the Pathology of the Liver

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It is generally agreed that the concentration and nature of fatty acids in the liver vary greatly in health and disease.[1] Changes are most marked when the liver itself is the site of the pathologic disorder.[2,3] Because of its importance in the metabolism of lipids, any disease of the liver will inevitably affect the pattern of the plasma lipids. During the past few years we have determined the plasma lipids in a group of patients with clinical evidences of liver disease, particularly cirrhosis of the liver, who later came to postmortem. We were, therefore, able to determine the liver lipids and to examine the state of the liver, thus making it possible to correlate plasma and liver lipids with the pathologic state of the liver. In some of the patients the vitamin A and carotene levels of the plasma and liver were also determined. Both of these substances are fat soluble and are present normally in the liver in considerable concentrations.[4,5]

All of the twenty-one subjects were patients on the wards of the Third (New York University) Medical Division, Bellevue Hospital. They were adults, their ages varying from twenty-one to seventy-four years; nine were females. Table I summarizes the clinical and laboratory findings other than the lipid, vitamin A and carotene determinations. All but three of the patients gave histories of alcoholism extending over a period of years. Cases 1 and 2 were not alcoholics and Case 13, who had diabetes mellitus, gave a history of limited alcohol intake. The clinical diagnosis of cirrhosis of the liver was made in all but Cases 1 and 2. Twelve of the patients were in poor nutritional state which in six cases had advanced to a state of emaciation. Of the nineteen patients with cirrhosis, 16 had ascites and 15 were jaundiced. As is to be expected, the albumin-globulin ratio was inverted in all of the patients with cirrhosis and the albumin levels were below the normal value.

The lipid values of the plasmas and livers are reported in Table II. The methods used for their determination have been reported previously.[6,7] The pathologic state of the liver is described in Table II in order to permit correlation with the lipid analyses. Protocols of the cases give the details. In order to facilitate discussion of the results the cases are divided into three groups: (1) those patients in whom there was an increase in the plasma lipids; (2) those patients with an increase in liver lipids and (3) patients in whom the only change was in the ratio of free to total cholesterol in the plasma. The relation of plasma to liver lipids is shown graphically for each group.

Group 1—*Plasma Lipids Elevated.* There were seven (Cases 1, 3, 4, 12, 13, 16 and 20) in whom the total plasma lipids were elevated. (Fig. 1.) This increase was shared by the other lipid fractions of the plasma with the exception of the total cholesterol which was not elevated in every case. In three (Cases 3, 4 and 16) the increase in plasma lipids was associated with a marked increase in liver lipids. In the livers, however, neither phospholipid nor total cholesterol fractions were involved in this

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increase. This is shown very clearly in the illustration. For comparison normal lipid values for both plasma and liver are given in Figure 3. The fact that the increase in plasma lipids was not associated with a consistent change in the concentration of liver

TABLE I

Case No.	Sex	Age	State of Nutrition	Alcohol Intake	Duration of Liver Symptoms	Ascites	Jaundice	Spider Angiomata	N.P.N. (mg. %)	Albumin / Globulin (Gm. %)	Total Protein (Gm. %)	Hematocrit (%)	Icteric Index	Bromsulphalein (%)	R.B.C. (millions)
1	M	52	Emac.	None	4 wk.	Moderate	Deep	No	.....	.....	....	....	.....	.....	5.4
2	F	54	Good	None	1 day	No	Deep	No	60–211	.....	....	....	55	.....	2.1
3	M	50	Good	30 yr.	2½ wk.	Yes	Deep	No	32	2.0/1.7	3.7	....	150	.....	2.5
4	M	47	Obese	7 yr.	4 days	Severe	Deep	No	75	2.2/2.5	4.7	....	135	.....	4.4
5	F	49	Emac.	3 yr.	2 wk.	Severe	Deep	No	30	.....	....	....	10	.....	2.0
6	F	24	Emac.	5 yr.	8 mo.	Severe	Deep	Yes	33–71	.....	....	....	40	.....	1.8
7	F	39	Emac.	Years	8 mo.	Yes	.....	No	30–53	3.0/4.1	7.1	....	21	.....	3.7
8	F	71	Emac.	Years	2+ yr.	Yes	Deep	No	32	2.2/3.9	6.1	....	60	.....	4.3
9	M	40	Obese	10 yr.	9 days	Yes	Deep	Yes	32	2.7/4.0	6.7	....	70	.....	3.4
10	M	50	Obese	Years	1 yr.	No	Yes and No	No	31	.....	....	....	12	.....	2.0
11	M	52	Emac.	Years	1 yr.	Severe	Yes	No	30–71	1.9/4.4	6.3	....	21	.....	3.4
12	M	61	Fair	Years	4 wk.	Yes	No	No	34	3.0/4.2	7.2	....	25	.....	4.5
13	M	49	Fair	Slight	2 yr.	Slight	Moderate	Yes	66	3.2/4.2	7.2	23	16	.....	4.0
14	M	45	Poor	26 yr.	4 wk.	Yes	Yes	No	24–61	2.7/4.4	4.5	39	72–30	.....	3.2
15	M	67	Poor	25 yr.	4 wk.	Yes	No	No	31–25	2.0/3.0	5.0	33–38	11	29–46	3.3
16	F	45	Poor	Years	3 mo.	No	Yes	No	19–63	2.5/3.0	5.5	27–22	.....	.....	1.5
17	M	61	Poor	21 yr.	2 yr.	Yes	No	No	30–67	1.4/4.6	5.5	39	16–24	44	3.6
18	F	57	Good	Years	4 wk.	Yes	Yes	No	30–55	1.8/4.5	6.3	39	25	42–28	3.4
19	F	50	Poor	Years	6 mo.	No	Yes	No	16	1.7/5.0	6.7	32	25	29	3.4
20	F	35	Poor	Years	2 yr.	Slight	.....	No	32	1.8/4.7	6.5	33	35	18	3.0
21	M	60	Good	Years	18 mo.	Yes	Yes	No	43	1.9/4.3	6.2	26	.....	23	3.8

lipids may have been due to the character of the pathologic change in the liver. For example, in Cases 1 and 13 the livers were both the seat of malignant changes, and in Case 1 this was so severe that there was practically no normal liver tissue left. It is interesting in this case that in spite of the widespread cellular change in the liver the ratio of free to total cholesterol in the plasma was normal. In the entire group of patients this was the only case in which this occurred. Case 13 was complicated by diabetes mellitus and, although this is often associated with fatty infiltration of the liver, in this patient there was no increase in liver lipids. In the other two cases in group 1, the liver in Case 20 was the seat of two pathologic processes and was grossly deformed. The left lobe showed the changes characteristic of portal cirrhosis and the right lobe was divided into several lobes by bands of fibrous tissue and was diagnosed as hepar lobatum. The patient had a history of syphilis and a positive Wassermann reaction. In Case 12 the plasma sample was taken seven days before death when the patient was still able to eat. Four days before death he became seriously ill and was unable to eat regularly. It may well be that the fat content of the liver decreased during this time and that the interval between the plasma and liver sample accounts for the lack of correlation between the lipid concentrations.

Group 2—Increase in Liver Lipids. The total fatty acids were greatly increased in the livers of Cases 3, 4, 5, 9 and 16. (Fig. 2.) In each case both the total fatty acids and the neutral fat fraction of the liver lipids increased. The phospholipids, however, were within normal limits, never exceeding 2.1 Gm. per cent. It is interesting that the phospholipid fraction was not affected in spite of the tremendous increase in total lipids. Examination of the plasma lipids of the five patients shows that the total fatty acids were elevated in only three (Cases 3, 4 and 16). Again, as in group 1, all of the lipid fractions of the plasma shared in the increase and the phospholipids were 260 mg. per cent or more. In Case 9, although the total plasma fatty acids were within the

TABLE II

Case No.	Days before Death	Blood Plasma Lipids: Total Lipids (mg. %)	Total Fatty Acids (mg. %)	Neutral Fat (mg. %)	Phospholipids (mg. %)	Cholesterol: Total (mg. %)	Esters (mg. %)	Free (mg. %)	Free / Total Ratio	Liver: Liver Weight (Gm. %)	Total Lipids Gm. %	Total Fatty Acids (Gm. %)	Neutral Fat (Gm. %)	Phospholipids (Gm. %)	Cholesterol: Total (Gm. %)	Free (Gm. %)	Histologic Findings in Liver
1	4	1108	718	409	259	281	224	57	20	4030	3.02	2.14	1.00	1.73	0.251	0.20	Liver architecture obscured by loosely arranged small cell (lymphocytic) lymphosarcoma; extensive fatty change in liver cords and radiating bands of connective tissue
2	5	....	...	...	...	87	35	52	60	....	.....	.....	.....	....	.....	....	The liver parenchyma is well preserved; no evidence of cirrhosis, no intrahepatic bile stasis, fatty deposits or inflammatory reaction
	4	548	397	260	197	73	26	47	64	....	.....	.....	.....	....	.....	....	
	3	....	...	...	...	76	27	46	61	....	.....	.....	.....	....	.....	....	
	2	....	...	...	...	97	16	81	84	1800	2.94	2.02	0.78	1.88	0.251	0.21	
3	16	1428	886	500	618	310	9	301	97	....	.....	.....	.....	....	.....	....	Mild monolobular type of portal cirrhosis with extensive fatty infiltration and focal evidence of bile stasis; there is focal necrosis of the fatty cells
	7	....	...	...	...	267	33	234	88	2990	12.8	11.20	10.2	1.97	0.490	0.26	
4	1	709	486	327	261	121	4	117	97	4000	15.5	14.00	13.8	1.26	0.360	0.26	Extensive fatty infiltration with early monolobular cirrhosis; widespread focal necrosis of fatty cells
5	10	247	150	51	145	46	8	38	83	1600	26.4	24.50	24.5	1.59	0.252	0.17	Advanced monolobular cirrhosis with extensive fatty changes
6	21	693	416	237	212	194	81	113	60	....	.....	.....	.....	....	.....	....	Advanced mono- and multilobular cirrhosis; some islands of liver tissue show considerable fatty change, others little or none; there is focal necrosis in the areas of advanced fatty changes
	15	640	...	204	231	173	46	127	73	....	.....	.....	.....	....	.....	....	
	8	683	...	223	198	193	97	96	50	....	.....	.....	.....	....	.....	....	
	3	....	...	...	...	190	103	87	46	1700	3.98	3.00	1.68	2.00	0.263	0.21	
7	15	444	278	157	131	114	59	55	48	1150	3.79	2.78	1.57	1.94	0.280	0.25	Advanced multi- and monolobular cirrhosis with minimal fatty changes
8	14	391	220	70	176	109	51	58	53	....	.....	.....	.....	....	.....	....	Advanced cirrhosis with a necrotic undifferentiated carcinoma
	6	407	...	101	181	102	33	69	68	....	.....	.....	.....	....	.....	....	
	4	404	235	101	169	108	36	72	67	940	3.19	2.36	1.43	1.41	0.290	0.20	
9	6	492	290	90	237	150	22	128	85	4000	14.7	13.1	13.10	1.24	0.290	0.16	Fatty cirrhosis, monolobular type; extensive fatty changes in liver cords and in radiating bands of connective tissue extending around portal areas and into and around lobules
10	1	200	121	56	79	50	36	47	57	3070	3.43	2.40	1.01	2.11	0.280	0.24	Advanced multi- and monolobular cirrhosis with moderate fat deposits
11	40	....	...	...	...	.82	29	53	65	....	.....	.....	.....	....	.....	....	Moderate multi- and monolobular cirrhosis with moderate fat deposits and severe focal necrosis of fatty cells
	4	330	201	94	127	83	36	47	57	1320	3.49	2.46	1.02	2.20	0.250	0.22	
12	7	862	616	457	204	162	85	77	48	1340	5.66	4.10	4.00	1.22	0.300	....	Advanced multi- and monolobular cirrhosis with minimal fatty changes
13	0	1384	868	472	541	314	180	234	75	3800	3.76	2.50	1.09	2.22	0.310	....	Liver cell type of carcinoma arising in advanced multilobular cirrhosis with practically no fatty change in surviving parenchyma
14	41	517	306	124	240	125	40	85	68	....	.....	.....	.....	....	.....	....	Advanced multi- and monolobular cirrhosis with extensive necrosis and some focal fatty change
	1	523	348	210	180	105	40	65	62	1450	4.78	3.60	2.45	1.90	0.290	....	

TABLE II.—(*Continued*)

Case No.	Days before Death	Blood Plasma Lipids								Liver Lipids							Histologic Findings in Liver
		Total Lipids (mg. %)	Total Fatty Acids (mg. %)	Neutral Fat (mg. %)	Phospholipids (mg. %)	Cholesterol				Liver Weight (Gm. %)	Total Lipids Gm. %	Total Fatty Acids (Gm. %)	Neutral Fat (Gm. %)	Phospholipids (Gm. %)	Cholesterol		
						Total (mg. %)	Esters (mg. %)	Free (mg. %)	Free / Total Ratio						Total (Gm. %)	Free (Gm. %)	
15	118	488	288	89	209	129	86	43	33	....	.....	.....	.....	....	.....	....	Moderate multi- and monolobular cirrhosis with minimal fat deposits; occasional portal area shows mononuclear cellular infiltration; slight bile duct proliferation
	91	....	...	...	...	137	88	49	36	....	.....	.....	.....	....	.....	....	
	81	....	...	...	...	155	98	57	37	....	.....	.....	.....	....	.....	....	
	59	....	...	...	...	148	88	50	34	....	.....	.....	.....	....	.....	....	
	20	492	268	57	216	150	87	53	35	....	.....	.....	.....	....	.....	....	
	0	380	252	58	179	103	55	48	46	1100	4.32	3.10	1.64	2.30	0.240	....	
16	24	1461	880	387	732	318	34	284	89	....	.....	.....	.....	....	.....	....	Extensive fatty change; mild monolobular cirrhosis with considerable loss of nuclear detail
	15	....	...	...	...	316	41	275	87	....	.....	.....	.....	....	.....	....	
	0	1397	880	482	587	297	44	253	85	5000	14.72	12.90	12.10	2.10	0.380	....	
17	52	493	260	52	203	162	107	55	35	....	.....	.....	.....	....	.....	....	Advanced multilobular cirrhosis; no fatty changes
	24	....	...	...	...	163	105	58	36	....	.....	.....	.....	....	.....	....	
	7	....	...	...	...	129	79	50	38	580	3.02	2.0	0.75	1.88	0.250	....	
18	77	450	264	108	159	128	77	51	39	....	.....	.....	.....	....	.....	....	Advanced multilobular cirrhosis; practically no fatty change
	45	....	...	...	...	159	100	59	37	....	.....	.....	.....	....	.....	....	
	18	....	...	...	...	177	119	58	33	1240	3.35	2.2	1.01	1.83	0.370	....	
19	6	541	300	97	213	165	93	72	44	1100	4.64	3.5	2.40	1.77	0.330	....	Advanced multilobular cirrhosis with islands of surviving hypertrophic liver cords with minimal fatty change
20	254	424	232	45	190	127	87	40	31	....	.....	.....	.....	....	.....	....	Two findings in liver—advanced portal cirrhosis in left lobe and hepar lobatum in right lobe
	10	....	...	...	...	80	55	25	31	....	.....	.....	.....	....	.....	....	
	1	589	428	286	175	88	56	32	36	1150	.....	4.1	3.10	1.70	.....	....	
21	43	....	...	...	...	200	119	81	41	....	.....	.....	.....	....	.....	....	Advanced multilobular cirrhosis with practically no fatty change; there is considerable focal necrosis
	15	....	...	...	...	200	111	89	45	....	.....	.....	.....	....	.....	....	
	3	412	266	35	148	189	113	76	41	2200	3.62	2.6	1.59	1.62	0.260	....	

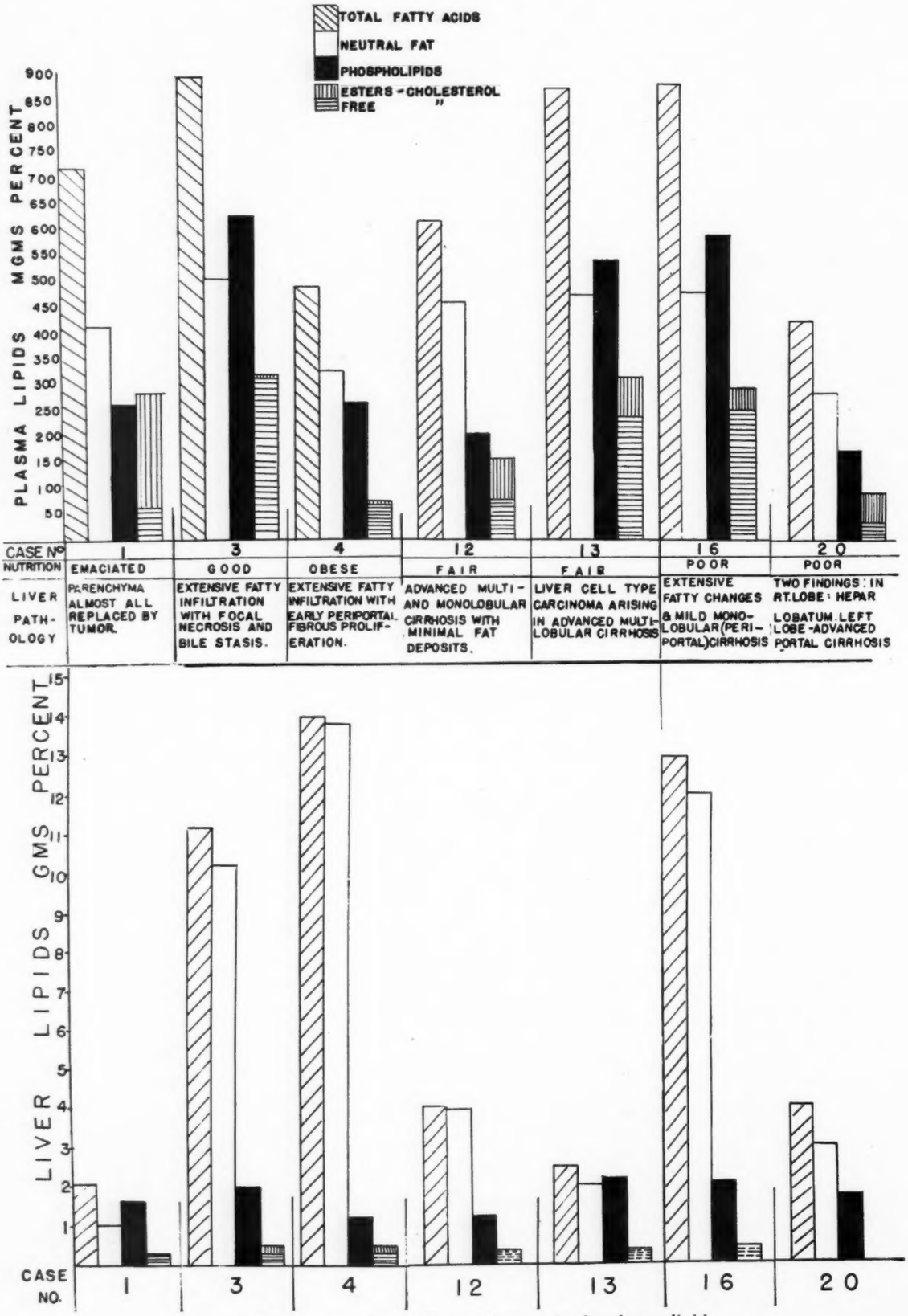

FIG. 1. Cases grouped according to increase in the plasma lipids.

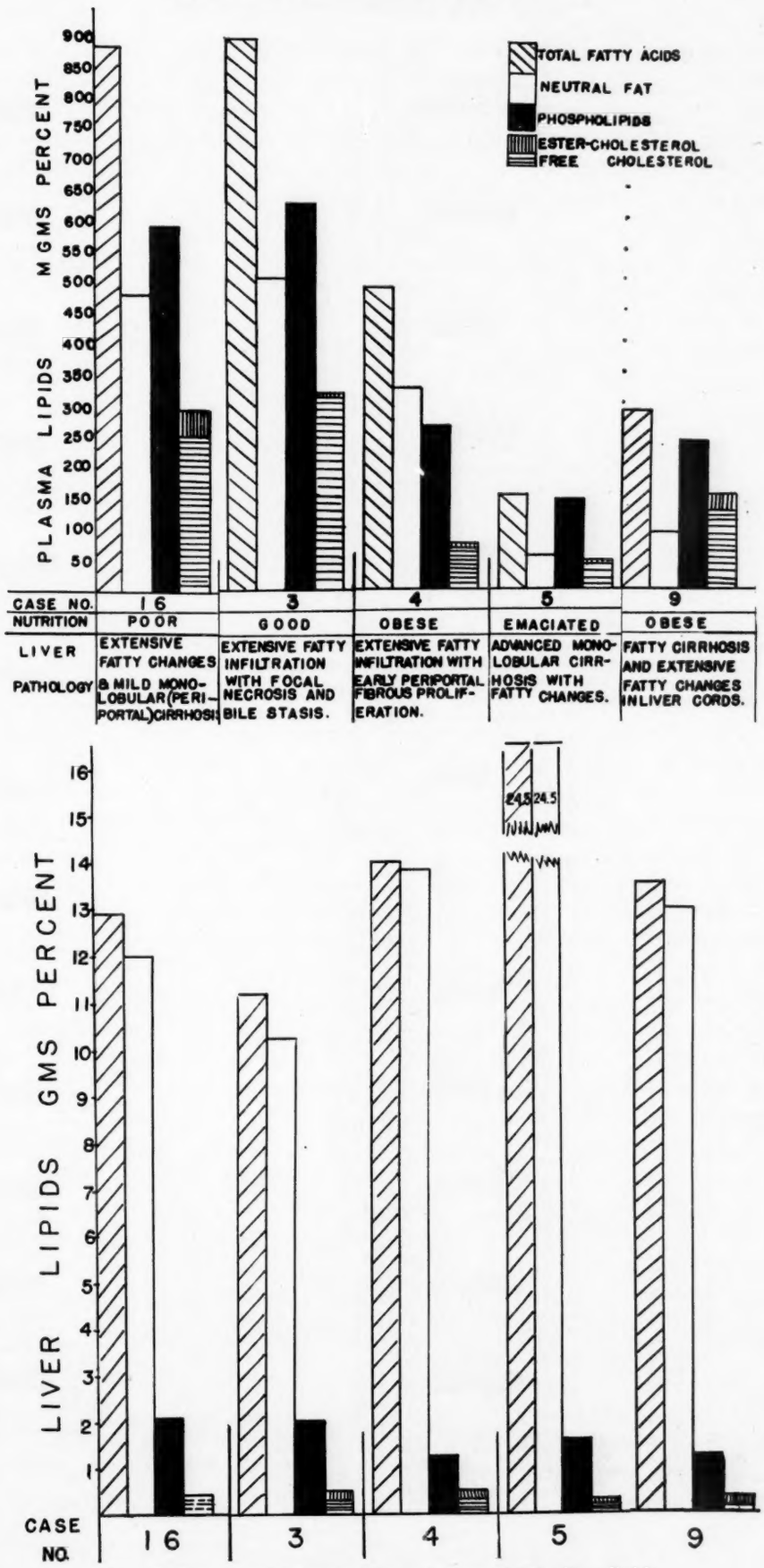

FIG. 2. Cases grouped according to increase in the liver lipids.

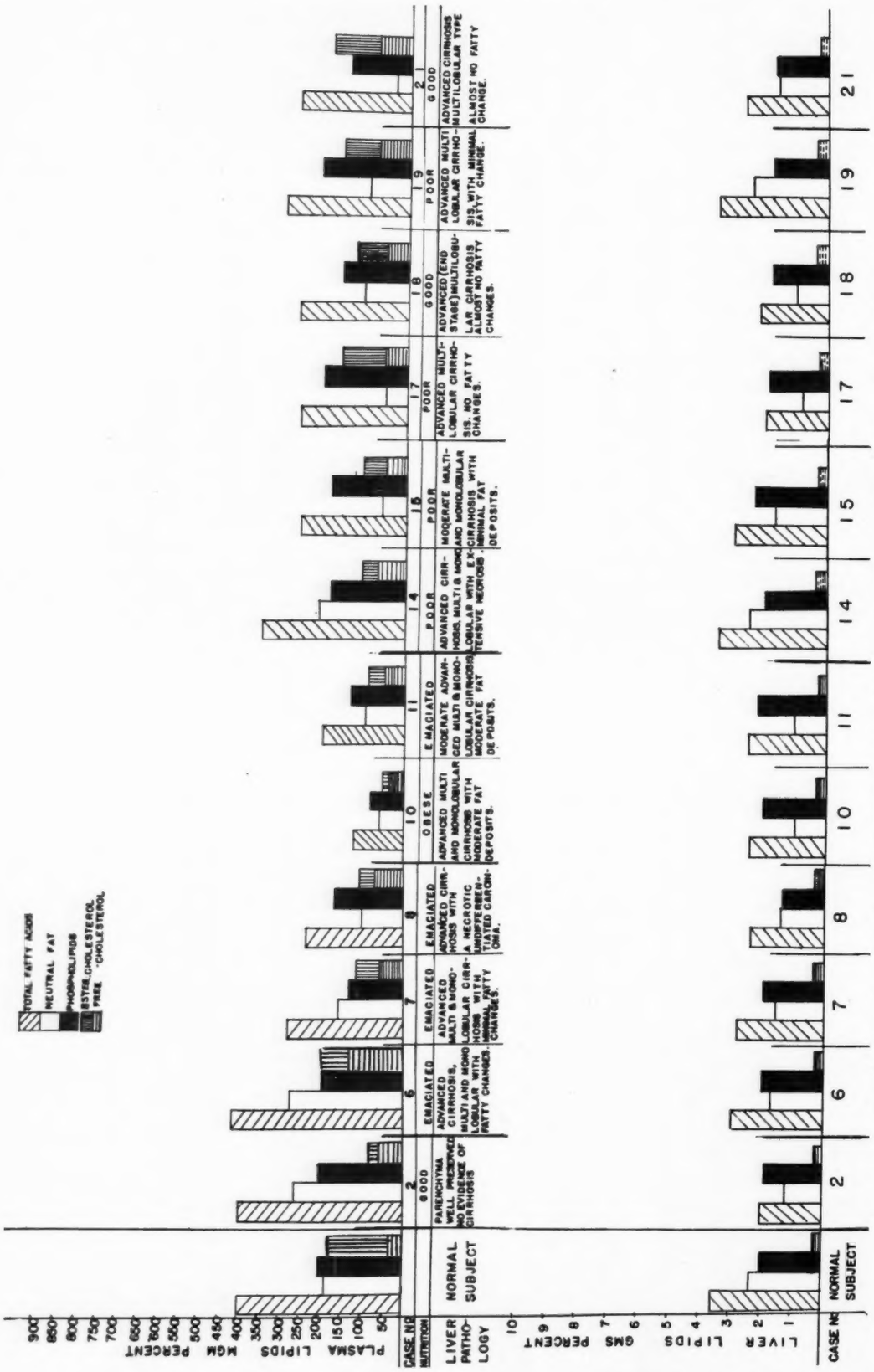

FIG. 3. Cases in which the only lipid change was in the ratio of free to total cholesterol in the plasma.

normal level, the phospholipid fraction was elevated (237 mg. per cent). In Case 5 there was no reflection in any fraction of the plasma lipids of the tremendous increase in liver lipids. Pathologically all of the livers showed extensive fatty changes and with the exception of Case 3 there were varying degrees of periportal cirrhosis. The nutritional status of the subjects was either good or obese in three (Cases 3, 4 and 9) but very poor in Cases 5 and 16. In this as in the previous group, one again encounters cases in which the changes in plasma and liver lipids do not parallel one another; in some cases in this group liver lipids were increased without any increase in plasma lipids. The time relation of the plasma sample to the liver sample varied from the day of death (Case 16) to ten days before death (Case 5). The latter case in which the liver lipid was the highest of any in the series, and in which the only alteration in plasma lipids was in the ratio of free to total cholesterol, was a patient who had been on an inadequate diet for six months prior to admission and who was emaciated. The fatty liver in this case therefore may have reflected the state of starvation, for experimentally starvation is associated with a decrease in plasma fatty acids rather than in increase.

TABLE III

RELATION OF LIVER LIPIDS TO WET AND DRY WEIGHTS IN SIX CASES

Case No.	Liver Weight (Wet) Gm.	Water (%)	Wet Weight (Gm. %)							Total Lipids Gm. per Liver Wet Weight	Liver Weight (Dry) Gm.	Dry Weight (Gm. %)					
			Total Fatty Acids	"Neutral Fat"	Phospholipids	Cholesterol Total	Cholesterol Free	Cholesterol (% free)	Total Lipids			Total Fatty Acids	"Neutral Fat"	Phospholipids	Cholesterol Total	Cholesterol Free	Total Lipids
1	4030	75.6	2.1	1.00	1.73	0.25	0.20	80.0	3.02	121.7	983.3	8.6	4.09	7.1	1.02	0.82	12.4
3	2990	68.2	11.2	10.2	1.97	0.49	0.26	53.6	12.8	383.3	950.8	35.3	32.1	6.2	1.54	0.82	40.3
4	4000	66.9	14.0	13.8	1.26	0.36	0.26	72.2	15.5	619.6	1324.	42.0	41.4	3.8	1.08	0.78	46.8
5	1600	54.5	24.5	24.5	1.59	0.25	0.17	68.0	26.4	422.4	728.	53.9	53.9	3.5	0.55	0.37	58.0
6	1700	78.3	3.0	1.68	2.0	0.26	0.21	80.8	3.98	67.7	368.9	13.8	7.8	9.2	1.2	0.97	18.3
9	4000	70.0	13.6	13.1	1.24	0.29	0.16	55.2	14.7	587.2	1200.	45.3	43.6	4.1	0.97	0.53	48.9

Group 3—The Only Lipid Change Was in the Ratio of Free to Total Cholesterol in the Plasma. In twelve patients the only striking change was in the ratio of free to total cholesterol. As we have previously reported, the ratio of free to total cholesterol in normal subjects does not exceed 29 per cent.[8] In all of the patients in this study, with the exception of Case 1, this ratio was above normal and in the patients in group 3 this was the only significant change. The total liver lipids in this group of patients were within normal limits. With the exception of Case 2 these patients all had varying degrees of periportal cirrhosis and the pathologic findings were so consistent that the microscopic sections from case to case revealed only the differences in degree of the process. The liver in Case 8 was also the seat of an undifferentiated carcinoma but, unlike Case 13, this did not affect the level of the plasma lipids. It should be recalled that in Case 13 diabetes mellitus was also present.

It is obvious from the results that absolute correlation between plasma and liver lipid fractions does not always occur in disease of the liver. One fact stands out in all of the plasma determinations, namely, that in cirrhosis and in fatty infiltration of the liver the ratio of free to total cholesterol is abnormal, and this occurs regardless of the level of the total cholesterol. This finding was so uniform that we believe the diagnosis of cirrhosis of the liver, with or without fatty infiltration, should not be made when

the ratio of free to total cholesterol is within normal limits. According to the method we have reported and according to the reports of Sperry,[8,9] this ratio normally does not exceed 29 per cent.

In six of the cases the per cent water of the liver was determined (1, 3, 4, 5, 6 and 9, Table III) and the lipid concentration was calculated on the basis of the dry weight of the liver. On the basis of the dry weight each fraction naturally was more concentrated, and the results show that when an increase in the total lipids and their fractions occurred it was an absolute increase. The relationship of the lipid fractions to one another remained unchanged.

Partition of the phospholipids (Table IV) was done in four of the livers (Cases 4, 5, 6 and 9) according to the method of Thannhauser et al.[10] In three of the four cases relative concentrations of lecithin, cephalin and sphingomyelin were very similar to those given by Thannhauser et al.[11] who reported an average distribution of 49, 47 and 4 per cent, respectively, in three normal human livers. The livers of Cases 4, 6 and 9 in the present series (Table IV) show percentile distributions which are very close to Thannhauser's figures. In the liver of Case 5, however, there was an apparent complete lack of cephalin. Since the calculation of cephalin is indirect and is largely contingent upon the accuracy of the choline determination, the latter was carefully checked and gave the value shown in the table. This is, of course, an unusual finding and it must be clearly borne in mind that it has been observed only in this one case. It will be of considerable interest to see whether further studies will support this finding. It is interesting that the liver in Case 5 presented other peculiarities, i.e., the lipid concentration was the highest of any case in the series but in spite of this the plasma fatty acids were not elevated; the water content of the liver was lower than in any of the other livers; and in spite of the tremendously elevated liver lipid the total weight of the liver was only 1,600 Gm. Pathologically, the liver of this case showed a very advanced degree of monolobular cirrhosis and clinically the patient was an emaciated individual. The data bear out again the observations of Terroine[12] that there is an irreducible minimum of fatty acid in the tissues and apparently this

TABLE IV

PARTITION OF PHOSPHOLIPIDS IN FOUR CASES

Case No.	Choline (mM %)	Phosphorus (mM %)	Choline Phosphorus	Phospholipids Total (Gm. %)	Sphingomyelin (Gm. %)	Mono Amino Phospholipids (Lecithin, Cephalin) (Gm. %)	Mono Amino Phospholipids (% of total)	Lecithin and Sphingomyelin (% of total phospholipids)	Cephalin (% of total phospholipids)	Sphingomyelin (% of total phospholipids)	Lecithin (% of total phospholipids)
4	1.04*	1.56*	.67*	1.26*	.....	....	....	67.0*	33.0*	†	(63.0)
5	1.57	1.52	1.03	1.23	0.044	1.19	96.8	100.0	0.0	3.2	96.8
6	1.70	2.39	.71	1.92	0.091	1.83	95.3	71.0	29.0	4.7	66.3
9	1.04	1.55	.67	1.24	0.066	1.17	94.7	67.3	32.7	5.3	62.0

All values are expressed on basis of wet weights.

* Analysis done on petroleum ether extract of lipid fraction.

Lecithin and sphingomyelin per cent of total phospholipid, calculated from choline phosphorus ratio.

Cephalin per cent of total phospholipid, calculated from choline phosphorus ratio.

Sphingomyelin per cent of total phospholipid, calculated from diaminophospholipid.

Lecithin per cent of total phospholipid, calculated from monophospholipid and choline phosphorus ratio.

† On assumption that sphingomyelin constitutes about 4 per cent of the phospholipids in this liver. Thannhauser.[10,11]

element consists of phospholipids resembling lecithin and cephalin in composition.

In eleven cases (9, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21) vitamin A and carotene were determined in the plasmas and livers. The methods used have been described previously.[13,14] The samples of liver were taken from all lobes, thoroughly hashed and mixed and a 5 Gm. aliquot was saponified under nitrogen; the vitamin A and carotene were extracted in the usual way. Following extraction vitamin A was determined in an

TABLE V

VITAMIN A AND CAROTENE VALUES OF PLASMA AND LIVER

Case No.	Days before Death	Plasma			Liver			
							Total in Liver	
		Vitamin A (mμ %)	Carotene (mg. %)	Liver Weight (Gm.)	Vitamin A (mμ %)	Carotene (mg. %)	Vitamin A (mμ)	Carotene mg.
9	6	8.0	.039	4000	None	0.20	None	8.0
12	6	7.5	.075					
	0	5.0	.063	1340	625.	0.13	8,375	1.7
13	180	18.0	.125					
	0	29.0	.156	3800	2225.	0.33	84,550	12.5
14	41	5.0	.050					
	1	6.0	.086	1450	100.	0.40	1,450	5.8
15	118	10.0	.072					
	85	12.0	.096					
	81	10.0	.108					
	59	10.0	.120					
	3	6.0	.090					
	0	5.0	.066	1100	860.	None	9,460	None
16	24	8.0	.067					
	15	10.0	.060					
	6	7.0	.096					
	0	6.0	.090	5000	42.	0.02	2,100	1.0
17	52	10.0	.144					
	24	10.0	.149					
	15	10.0	.132					
	7	7.2	.108					
	0	5.0	.100	580	3514.	0.21	20,381	1.2
18	77	6.0	.060					
	18	12.0	.120	1240	666.	0.16	8,258	2.0
19	6	12.0	.075	1100	600.	0.17	6,600	1.9
20	50	4.8	0					
	32	2.4	0					
	10	5.0	.012					
	1	2.4	0	1150	None	None	None	None
21	43	11.0	.120					
	15	5.0	.120					
	3	5.3	.120	2200	155.	0.08	4,805	1.7

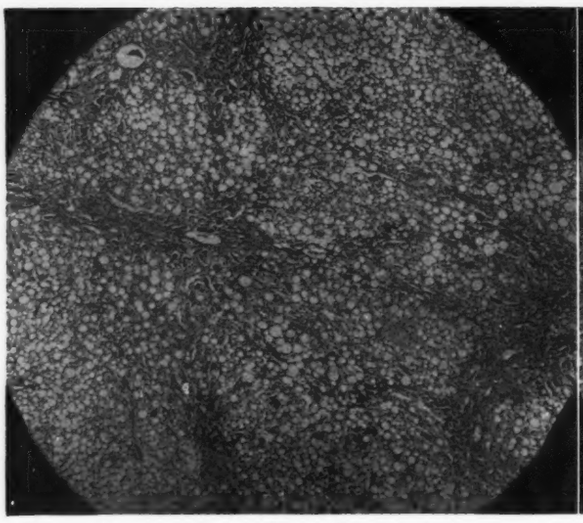

FIG. 4. Case 5. Advanced monolobular cirrhosis and extensive fatty change. Liver weight, 1,600 Gm.; total lipids, 26 Gm. per cent.

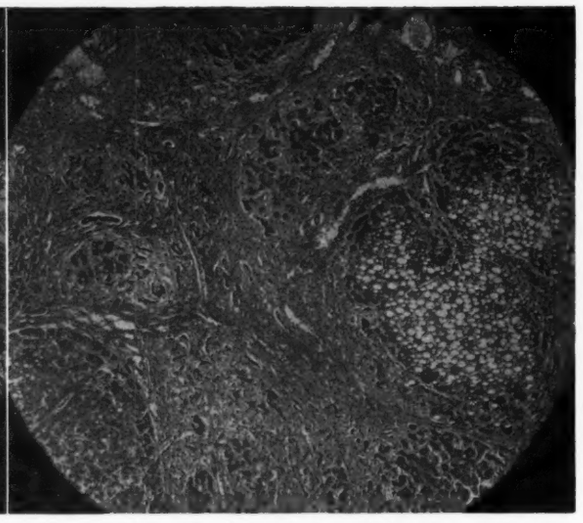

FIG. 5. Case 19. Advanced multilobular cirrhosis. Minimal fatty change. Liver weight, 1,100 Gm.; total lipids, 4.6 Gm. per cent.

Evelyn photoelectric colorimeter which had been standardized with crystalline vitamin A using a 620 mμ filter. This was a change from the method originally used and made it possible to report the values for vitamin A in micrograms. The plasma values for vitamin A were, as was to be expected, well below the normal level.[13] In a group of twenty normal males plasma values for vitamin A ranged from 48 to 33 micrograms per cent, the average being 38 micrograms per cent. In this group with cirrhosis of the liver the vitamin A levels of the livers ranged from 2.4 to 29 micrograms per cent with an average of 8.4 micrograms per cent. Carotene values averaged .085 mg. per cent with a range from 0 to .156 mg. per cent, the latter being in Case 13 who had diabetes mellitus. These values are also somewhat below the normal range of .085 to .230 mg. per cent. (Table v.)

The pathologic changes in the livers of the patients were so characteristic of the already well described lesions of periportal fibrosis that it would be redundant to publish microphotographs of all the cases. The microphotographs of the microscopic sections of two cases are shown which illustrate the character of the pathologic changes observed. Case 5 (Fig. 4) showed advanced monolobular cirrhosis of the liver as well as extensive fatty changes. This was the liver in which the total lipids were 26 Gm. per cent although the weight of the liver was only 1,600 Gm. The microphotograph of the microscopic section of Case 19 (Fig. 5) showed advanced multilobular cirrhosis with minimal fatty change. Total liver lipids in this liver were 4.6 Gm. per cent and the weight of the liver was 1,100 Gm.

COMMENT

These observations on lipid fractions in the plasmas and livers of the same patients show that there is no absolute correlation between the amounts of total fatty acids in the plasma and in the liver. As can be seen in the figures, total fatty acids in the plasma may be elevated without a regularly associated increase in the concentration of fatty acids in the liver. The interval of time elapsing between the taking of the blood sample and the liver sample is naturally of considerable interest because of the possible influence of the time interval on the relationship of the lipid fractions. (See Table II.) In cases in which it was possible to do repeated fractionations of plasma lipids (Cases 6, 8, 14, 15, 16 and 20),

the time intervals varied from 254 days to the day of death, thus making it possible to evaluate the consistency of the relationship between plasma and liver lipids over a considerable period. In some of the cases plasma samples analyzed shortly before death showed a definite increase in the ratio of free to total cholesterol, suggesting a diminishing functional capacity of the liver in respect to the esterification of cholesterol. This, however, was not always the case as is shown in Case 6 in which the ratio of free to total cholesterol fell from a peak of 73 per cent on the fifteenth day before death to 46 per cent on the third day before death. Total plasma lipids remained fairly consistent on repeated analyses. In Case 20 in which the original determination had been done 254 days before death, the total lipids rose from 424 mg. per cent to 589 mg. per cent, and the total fatty acids rose from 232 mg. per cent to 428 mg. per cent. The results in the majority of cases suggest that once the liver is severely damaged the alteration in the plasma lipid fractions remains relatively constant. In none of the cases was there any significant clinical improvement during the course of therapy, which consisted of a highly nutritious diet and large doses of vitamin B complex. In some patients in whom clinical improvement and recovery of liver function had occurred the ratio of free to total cholesterol had returned to within normal limits after a considerable period of time.[21]

The discrepancy in the concentration of plasma and liver lipid fractions in patients with chronic liver disease does not seem to us surprising. In the experimental animal more constant results in the relation of plasma and liver lipids may be expected, because liver disturbance is fairly acutely produced and the method of producing liver damage is usually by means of a diet deficient in choline. In the patient with chronic liver disease the situation is entirely different and the process has undoubtedly been going on for years. By the time the patient comes under observation he is severely ill and often in a terminal state. Furthermore, as is demonstrated in the pathologic examination of the liver, the derangement is advanced and fibrosis and replacement of normal liver tissue is a conspicuous finding. One is therefore making observations at a time when the function of the liver is affected, both because of inadequate amounts of substances such as choline and because of profound destruction of liver tissue. The possibility exists also that when liver lipids are elevated with no change in the concentration of plasma lipids the liver damage has progressed to an extent where the phospholipid turnover in the liver has been blocked. Chaikoff[16] has reported that as a result of experiments in which P^{32} was injected into animals the entrance of fat into the liver and its release from the liver have been linked with the rate of lipid phosphorylation. The effect of choline was to stimulate the rate of phospholipid turnover and this effect was observed despite the fact that the content of total phospholipid in the liver showed no measurable change. It is the opinion of other investigators[17,18] that the incorporation of phosphate into phospholipid molecules of plasma occurs for the most part in the liver. Fishler[19] studied lipid phosphorylation in the hepatectomized dog. This was done by injecting inorganic P^{32} intravenously immediately after removal of the liver. Almost no phospholipid P^{32} was recovered in the plasma as late as three to six hours after hepatectomy. The amounts of injected P^{32} that had been incorporated into phospholipid of the kidneys and of the whole small intestine were approximately the same as those obtained from these tissues in normal animals. These observations support the idea that the main site of phosphorylation of plasma phospholipid is the liver. Hahn and Hevesy[20] found that in perfusion experiments with labelled sodium phosphate in cats that lipemic blood was more effective in the formation of phosphatides in the liver than was normal blood. They interpret this to mean that lipemic blood stimulates phosphatide formation in the liver, and they go on to say that as

lipemic blood is changed into normal blood the excess phosphatides are taken up by the liver until "normal" phosphatide content of the blood is reached. In the patient with cirrhosis of the liver the first stage of the disease is probably that of fatty infiltration and at this point the liver is under considerable stress to maintain a rate of phosphorylation that will keep the plasma lipid fractions normal. Obviously as it fails to do this more and more fat is piled up in the organ and circulation to the liver cells is impaired with consequent necrosis. Eventually the liver is so badly damaged that the patient is in much the same state as the hepatectomized dog and in respect to lipid metabolism this means that phosphorylation is impaired and the plasma lipids may be low and fail to reveal changes in the liver lipids. The nutritional status of the patient and the duration of the symptoms of liver disease may also bear some relation to the disturbances evident in the plasma lipids. For example in Figure 1 the symptoms of liver disease were of short duration in Cases 3, 4, 12 and 16. Cases 3 and 4 were obese and showed no evidence of malnutrition. Case 13 in this group was in a fair nutritional state although the symptoms of liver disease dated back for two years; this patient also had diabetes.

Peters and his collaborators[15] fractionated the plasmas in a group of patients with various types of liver disease and in nine of these patients liver biopsies were done and the liver lipids were also fractionated. The changes in liver lipids of these nine patients (seven had either fatty infiltration of the liver or cirrhosis, one had a carcinoma of the pancreas, and in the remaining patient the liver was normal) showed the same pattern as we have observed. The fatty acids in the liver were above normal limits in three of his patients, and in the plasmas of those patients the range in the serum fatty acids was from 9.5 to 26.2 mEq./L. Obviously in his cases, as in ours, there was no absolute parallelism between the concentration of fatty acids in the serum and in the liver.

The most reliable index to the pathologic state of the liver is the ratio of free to total cholesterol in the plasma and, as shown in Figures 1 to 3, in all of the patients with cirrhosis this ratio was inverted regardless of the amounts of total cholesterol. Peters et al.[15] observed this same change in their patients with portal cirrhosis. They also reported that the cholesterol fraction was usually low or normal. In the patients in our study the cholesterol fraction was elevated when the other lipid fractions were elevated, with the exception of two cases.

We observed as have Peters et al.[15] that plasma phospholipids in general parallel the total plasma cholesterol in patients with liver disease. In the cases we studied this ratio was quite constant but as the phospholipids rose the proportional rise in total cholesterol was not as great. This relationship was not apparent when the liver phospholipid was plotted against the total cholesterol in the liver.

Neither vitamin A nor carotene levels in either plasmas or livers bore any relationship to the concentration or distribution of the fatty acids. Although the metabolism of these fat-soluble substances is profoundly disturbed in patients with cirrhosis of the liver, the mechanism of this disorder is probably not the same as that which controls the fatty acid disturbance. In only two cases was the total amount of vitamin A in the liver high (Cases 13 and 17). One of these (Case 13) had diabetes mellitus and the plasma levels of both vitamin A and carotene were the highest of any in the series. The carotene concentration in the liver of this patient also was increased. Case 17 received large doses of vitamin A intramuscularly and this undoubtedly affected the vitamin A concentration in the liver.

SUMMARY

The plasma and liver lipids were determined in twenty-one subjects, nineteen of whom had cirrhosis of the liver. All of the subjects were adults and nine were females. Of the nineteen patients with cirrhosis, sixteen had ascites and fifteen were jaundiced. The liver samples were obtained at post-

mortem. The time interval between the blood and liver samples varied from twenty-four hours to 254 days. The values for the various lipid fractions over these periods of time were altered significantly in only one case. None of the patients improved clinically to any significant extent during the period of observation.

The most consistent and outstanding change in the plasmas in all of the patients with cirrhosis of the liver was the alteration of the ratio of free to total cholesterol which was inverted in every instance. Plasma lipids were elevated in seven cases, and in three patients this was associated with a marked increase in the liver lipids. In a total of five cases liver lipids were greatly increased. In twelve patients the only significant change in lipid distribution in the plasma was in the ratio of free to total cholesterol.

The per cent water was determined in the livers of six patients. When lipid fractions were calculated on the basis of the dry weight of the liver, their relation to each other was unchanged.

Partition of the phospholipids was done in four of the livers, and the relative concentrations of lecithin, cephalin and sphingomyelin in three of these cases were very similar to those reported by Thannhauser and showed an average percentile distribution of phospholipids of 63.3, 31.6 and 5.0 per cent, respectively.

Vitamin A and carotene levels were determined in the plasmas and livers of eleven of the cases. Vitamin A levels in plasma were uniformly low and carotene was also below normal levels in most of the cases. In all but two of the livers the vitamin A and carotene levels were below normal values.

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Renal Tubular Excretory Capacity for Penicillin in Health and in Subacute Bacterial Endocarditis*

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It has been amply shown that penicillin is largely excreted by the kidneys without appreciable destruction in the body[1] and that this process occurs rapidly[1] thus playing an important part in limiting the usefulness of that drug in the treatment of infection.

The belief that penicillin leaves the kidneys not only through glomerular filtration but also by tubular excretion has been substantiated by the work of Rantz and Kirby[2] on penicillin clearances. These investigators showed that the amount of blood cleared of penicillin by the kidneys per minute compared with that cleared of diodrast, another substance excreted by the renal tubules.[3] In addition the clearance values of penicillin are far higher than those of such drugs as inulin which is known to be excreted solely by glomerular filtration. Rammelkamp and Bradley,[4] who showed that elimination of penicillin is retarded when penicillin and diodrast are given simultaneously, suggested that there existed between these two drugs a competition for the same mechanism of tubular excretion. This has also been shown to be true of para-aminohippuric acid.[5]

It was of practical importance, therefore, to know the maximal tubular excretory capacity (TM_P) of the kidneys for penicillin since doses of the drug surpassing TM_P would be expected to produce relatively more rapid rises in the blood levels of penicillin than amounts under this level.

It is already known that with renal damage penicillin excretion is hindered along with other renal functions and that high and sustained blood levels may follow relatively small doses.[6] In diseases in which renal damage occurs and which are susceptible to treatment with penicillin renal failure might then paradoxically exert a favorable influence on the direct outcome of the illness. One disease to which these events are applicable is subacute bacterial endocarditis which in most cases has been found highly amenable to penicillin and in which a high percentage of cases has more or less renal damage.[7]

It is of interest then to know of how much importance the renal damage in subacute bacterial endocarditis is in producing higher than usual blood levels of penicillin. Loewe, Rosenblatt and Alture-Werber[8] found that in a case of a patient with resistant endocarditis receiving large doses of penicillin by continuous intravenous drip the serum levels of penicillin began to rise above the expected levels when a dose of 625,000 units per hour was reached. It was suggested that at this dosage the TM of penicillin had been attained. It has been shown that with lower continuous intravenous dosages the rise in serum penicillin concentration is directly proportional to the increase in dose.[2] With these points in mind, serum levels, urinary excretion and serum clearances of penicillin in normal individuals and in patients with subacute bacterial endocarditis have been studied.

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METHODS AND MATERIALS

Penicillin Determination. The concentration of penicillin in serum and urine samples was determined by the tube dilution method of Kirby and Rantz,[9] a modification of the Rammelkamp technic.[10] The blood samples were collected and the serum removed aseptically. The urine was passed through a Seitz filter. When delays occurred in performing the determinations, the samples were kept in a frozen state in the dry ice refrigerator. Two or more determinations were made on each sample and when results differed they were averaged.

Administration. Crystalline sodium or potassium penicillin was dissolved in 500 cc. of isotonic saline in all but two instances and administered intravenously at as constant a rate as possible. The times of commencement and completion of each dose were recorded. Subjects received only water after the evening meal of the preceding day and were required to fast and to force water by mouth during the procedure. Those patients receiving intramuscular penicillin prior to the test were given their last dose not less than six hours previous to the beginning of these studies.

Urine. Collection of urine specimens began not less than thirty minutes after starting the intravenous administration of penicillin, with two exceptions: Subject P, dose No. 2, after twenty-five minutes, and Subject T, dose No. 3, after sixteen minutes. Specimens were collected over a timed period of thirty minutes or more except in two instances: Subject T, dose No. 1, twenty-six minutes, and dose No. 3, nineteen minutes.

Blood. Two samples were collected, one at the beginning and one at the end of each urine collection in Subjects B, C, E and T (Dose Nos. 4 and 5). One sample was collected at the midpoint of each urine collection period in Subjects P, C, B and T (Dose Nos. 1, 2 and 3).

TABLE I

CLINICAL DATA ON SUBJECTS STUDIED

Subject	Age	Surface Area (sq. m.)	Diagnosis	Urinary Studies*										Remarks
				Blood Urea (mg. %)	PSP Excretion†		Volume (cc. per 24 hr.)	Specific Gravity	Reaction	Protein (Gm. per 24 hr.)	White and Epithelial Cells (million per 24 hr.)	Red Cells (million per 24 hr.)	Casts (100,000 per 24 hr.)	
					Time min.	Per cent								
P	43	1.56	Subacute bacterial endocarditis	50	81	30	1044	1.014	....	1.168	24	20	32	No cardiac failure; heart normal size
G	54	1.89	Subacute bacterial endocarditis Mild hypertension	62	120	27	2520	1.010	....	0.762	2	128	2	No cardiac failure; heart normal size
R	43	1.93	Subacute bacterial endocarditis	25	120	80	1644	1.014	....	0.000	4	0	0	No evidence of cardiac failure except slight cardiac enlargement
T-test 1	41	1.62	Subacute bacterial endocarditis	35	120	80	504	1.024	Acid	0.036	1	1	0	Moderate cardiac enlargement but no other evidence of failure
T-test 2	..	....	Relapsed subacute bacterial endocarditis	..	120	75	432	1.024	Acid	0.032	0	0	0	Heart a little larger, otherwise the same
E	48	1.61	Gumma of the skin	27	120	85	1368	1.019	....	0.000	9	3	1	Marked secondary infection of gumma Poor cooperation in forcing fluid
C	28	1.86	Healthy	33	120	75	1117	1.016	Acid	0.042	1	0	0	No history of renal disease
B	31	2.00	Healthy	30	120	70	1014	1.017	Acid	0.039	1	0	0	No history of renal disease

Time elapsed between tests 1 and 2, patient T, seventy-nine days.
* Addis count.
† 6 mg. PSP injected intravenously at start of test.

Sources of Error. Penicillin determinations in samples of high concentration were at times inaccurate because as the higher levels were reached the difference in penicillin concentration between two consecutive tube readings was large (up to several thousand units). In cases in which there seemed to be an obvious discrepancy the samples were reassayed and interpolation dilutions were made between the two penicillin concentrations in question.

Some of the patients had difficulty in voiding and urine collection periods ran past the termination of the intravenous drip. These periods, however, were never longer than a few minutes.

The rate of flow of the solution was not constant at all times. An attempt was made to administer the penicillin to Patients P, G, R and T (Dosage Nos. 1, 2 and 3) over a predetermined period thus necessitating occasional acceleration or retardation of the intravenous drip. Subsequent determinations were made at an almost constant speed of delivery with a calibrated Murphy drip, making it possible to administer the solution in the approximate

TABLE II

ABSORPTION, EXCRETION AND CLEARANCE OF INTRAVENOUSLY ADMINISTERED PENICILLIN

Subject	Dose No.	Penicillin Administered (units per hr.)	Urine			Serum Penicillin Concentration (units per cc.)	Clearance
			Excretion (cc. per min.)	Penicillin (units per cc.)	Penicillin Excretion (units per min.)		Serum Cleared of Penicillin (cc. per min.)
P	1	40,246	4.80	66	317	2.00	158
	2	500,000	5.50	500	2750	20.00	135
G	1	50,000	7.47	100	747	5.00	149
	2	100,000	7.73	100	773	5.00	155
	3	500,000	5.77	400	2308	20.00	116
R	1	50,000	11.10	50	555	1.00	555
	2	100,000	10.89	100	1089	1.00	1089
	3	546,000	13.66	400	5464	10.00	546
T	1	44,760	11.35	20	227	1.00	227
	2	263,500	9.84	100	984	10.00	98
	3	1,621,000	11.05	500	5525	50.00	111
			79 days elapsed				
	4	63,500	8.08	100	808	2.00	404
	5	351,500	6.08	600	3648	15.00	243
E	1	50,000	0.68	1000	680	0.80	850
	2	411,000	0.68	6000	4080	10.00	408
	3	2,050,000	0.55	30000	16500	100.00	165
	4	4,720,000	1.67	40000	66800	300.00	223
C	1	45,780	9.30	59	544	0.50	1088
	2	411,000	4.43	1400	6202	6.38	972
	3	774,180	6.03	1750	10553	12.50	844
	4	1,655,160	5.52	4000	22080	25.00	883
	5	3,318,000	11.49	4500	51700	91.50	565
	6	4,900,000	9.06	6666	60393	150.50	403
B	1	58,200	13.98	31	433	0.76	570
	2	504,000	8.37	666	5570	9.50	586
	3	892,000	9.74	1250	12180	18.75	650
	4	1,790,000	4.84	6666	32120	60.50	533
	5	3,650,000	14.68	2000	29360	91.50	321
	6	4,025,000	1.93	30000	57900	150.00	383

period desired without changing the rate of flow.

Subjects. Patients P, G, R and T were under treatment for subacute bacterial endocarditis proven by blood culture.

Patient E, with a diagnosis of tertiary syphilis of the skin with secondary infection, was chosen as a control but his debilitated condition, age forty-eight, and failure to excrete large quantities of urine probably exclude him from this group.

Patients C and B were normal young men in good health. Patients P and G had clear evidence from their urinary studies and phenolsulfonphthalein excretion values of renal lesions while patients T and R gave no indication of renal disease. (Table I.)

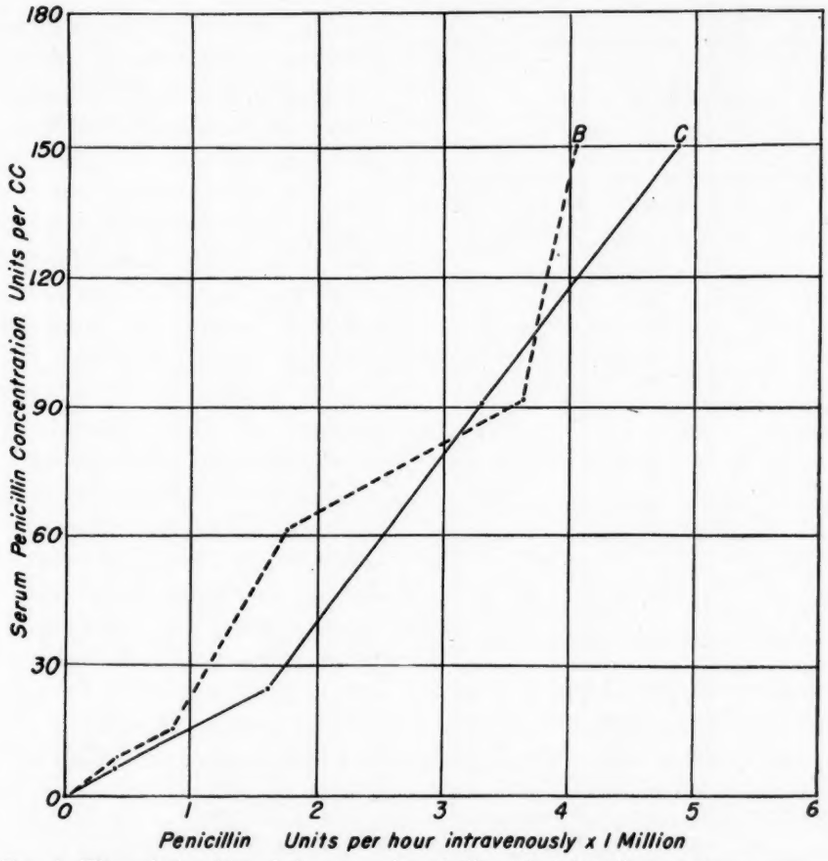

FIG. 1. The relationship of the rate of penicillin administration to serum concentration in healthy people.

RESULTS

The rate of penicillin administration by the intravenous route was computed as units per hour. The rate of excretion and serum levels of penicillin (Table II) with each dosage in each subject furnished the data for determinations of serum clearances. The rate of urine flow was found to bear no relationship to the per cent of penicillin excreted, and as large a portion of the dose was excreted with a urine flow of 0.68 cc. per minute (Subject E, dose No. 1) as with a flow of 9.74 cc. per minute (Subject B, dose No. 3). The per cent of penicillin excreted appeared to depend on renal function rather than on the forcing or withholding of fluids.

Table II shows that there are a number of inconsistencies in the penicillin blood and urine concentrations and resultant clearances, and that the absolute values are not as significant as are the trends. Nevertheless, it is possible to draw some clear cut conclusions from these values.

Serum Concentrations. It has been found[11] that with continuous intravenous adminis-

tration a plasma level of 1 unit per cc. results from a dose of approximately 41,000 units per hour, and that this level increases in direct proportion to the increase in dosage. Thus, a dose of 410,000 units per hour produces a level of 10 units per cc.

TABLE III
SERUM PENICILLIN CONCENTRATIONS IN NORMAL HUMANS

Subject	Penicillin		
	Intravenous Dose (units per hr.)	Actual serum Concentration (units per cc.)	Expected Serum Concentration (units per cc.)
C	45,780	0.50	1.09
	411,000	6.38	10.01
	774,000	12.50	18.43
	1,655,160	25.00	40.37
	3,318,000	91.50	80.93
	4,900,000	150.50	119.51
B	58,200	0.76	1.42
	504,000	9.50	12.30
	892,000	18.75	21.50
	1,790,000	60.50	43.70
	3,650,000	91.50	89.02
	4,025,000	150.00	98.05

The two normal controls, C and B (Fig. 1 and Table III) attained serum levels close to the expected values with the lower dosages, but with doses of 4,025,000 units (B) and 4,900,000 units (C) per hour the levels were considerably higher. This indicates that the maximum tubular capacity of the kidneys for penicillin had been reached.

The serum concentrations of penicillin in the other patients varied. (Table II.) Those of Subjects R and T were within a normal range. Those of Subjects P and G were higher, pointing to a reduction in their TM_P. The two large doses received by Subject E produced levels well above the expected values, indicating that his TM_P also was reduced. Figure 2 demonstrates these relationships in both normals and patients.

Clearances. Figure 3 shows the rates of renal clearance of penicillin at various dosage values in healthy and sick human beings. Assuming that clearance values for penicillin below TM_P are the same as those for diodrast below TM_D, the lower limit of normal should be 561.1 cc. of serum cleared of penicillin per minute (normal males corrected to a surface area of 1.73 square meters).

The clearances were above this figure in the two normals, C and B, with the lower dosages of penicillin. Whether this is due to errors in the dilution technic for penicillin determination or to differences in tubular mass is not known but the consistently higher curve of Subject C probably means that this TM_P was considerably greater than that of B. (Diodrast clearances in healthy males may vary by as much as 271.8 cc. of plasma per minute.)[3] Clearances began to drop sharply between dosages of approximately 1,500,000 and 3,500,000 units of penicillin per hour.

Patient R's clearances were also normal and his TM_P was probably not reached since the first and last values were approximately the same. The wide variation in his figures may be attributed to technical error. Subject E's initial clearance, which was similar to those of the normals, dropped below this level with a dosage of only 411,000 units of penicillin intravenously per hour, suggesting that he did have a diminished tubular excretory capacity. Patients P and G whose renal studies were grossly abnormal showed very low clearances, a finding compatible with their relatively high serum penicillin concentrations. Although the renal studies of Patient T were normal, his clearances on two occasions were abnormal. The fact that his serum penicillin concentrations were, for the most part, higher than expected suggests that he did have decreased renal function.

COMMENTS

The data presented above have confirmed previous work showing that penicillin* is excreted by the kidney tubules. For normal males the maximal tubular capacity has

* The penicillin used in this study was generously donated by the Commercial Solvents Corp.

been found to lie between 1,655,160 and 3,650,000 units of penicillin intravenously per hour. Since the serum concentrations attained with dosages of 3,650,000 (B) and 3,318,000 (C) units of penicillin per hour were still approximately the expected levels with that dosage, it can be assumed that TM_P actually lies much closer to 3,650,000 than to 1,655,160 units of penicillin administered intravenously per hour. After TM is reached tubular excretion can no longer increase by definition and, therefore, any increase in excretion resulting from doses above TM must result from an increase of the drug in the glomerular filtrate. The result would be a relatively precipitous rise in the serum concentration of penicillin. Since this rise did not occur with doses in the neighborhood of 3,500,000 units per hour and since the sharp drop in clearance values occurred somewhere between that dose and the previous lower dose, it may be concluded that approximately 3,000,000 units of penicillin per hour intravenously, or 50,000 units per minute, is the TM of penicillin. The crystalline penicillin used contained 1,600 units per mg. Therefore, the maximal tubular excretory capacity of normal kidneys for penicillin is approximately 30 mg. per minute, or 1,800 mg. per hour.

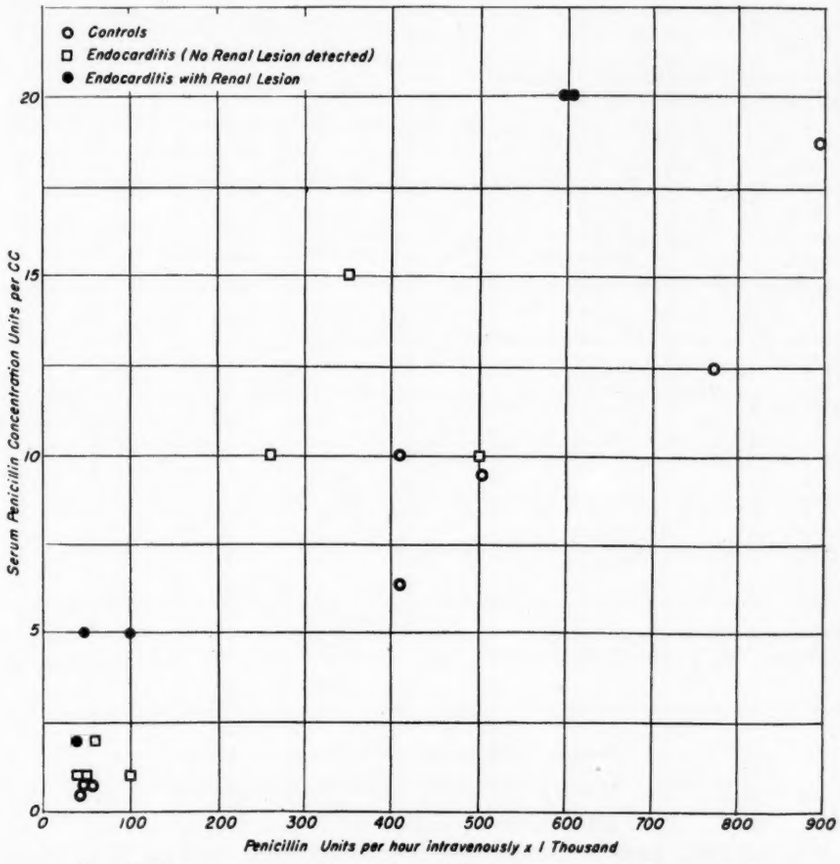

FIG. 2. Serum concentrations of penicillin in sick and healthy people.

The same conclusions may be reached by the calculation of glomerular and tubular excretion of penicillin at each dosage level. Using the data of Table II and the value of 131 cc. per min. per 1.73 square meters of surface area[3] as the glomerular filtration rate, in Subject C it was found that the ratio of tubular to glomerular excretion of penicillin for the first four doses lay between 7.8 and 6.0. On the fifth dose it dropped to 4 and on the last dose to 2.9.

In Subject B the ratio varied from 3.5 to 4.3 for the first four doses, dropping to 2.1

and 2.5 on the fifth and sixth doses, respectively. Therefore, on the fifth dose in each patient, while the glomerular filtration of penicillin continued to rise in proportion to the serum concentration, the tubular excretion failed to increase correspondingly as

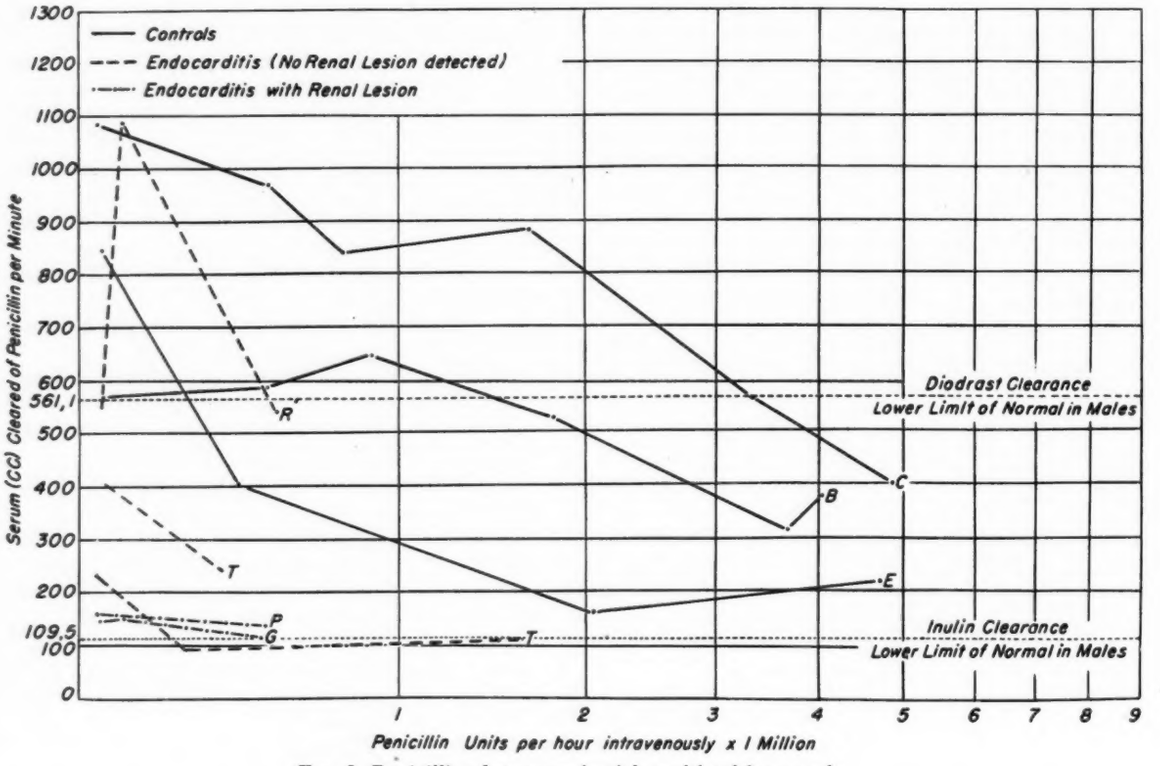

FIG. 3. Penicillin clearances in sick and healthy people.

it had in the lower doses. This again places the TM of penicillin below 3,318,000 and 3,650,000 units of penicillin per hour intravenously and above 1,655,160 and 1,790,000 units per hour.

While the clearances of one patient with subacute bacterial endocarditis were normal, those of three others and of a patient with tertiary syphilis were depressed. In two of these latter patients there were obvious renal lesions. In one, G, whose infection was caused by a highly resistant organism and who was treated with 12,000,000 units of penicillin per day for sixty days, the renal lesion was of distinct benefit since very high levels of penicillin were obtained in his serum.

Patient T whose renal studies were normal during life was similar to some of the cases mentioned by Christian[7] who in spite of normal renal sediments were found at autopsy to have fibrinoid glomerular thrombi and renal infarcts. At autopsy patient T's kidneys showed a mild diffuse glomerulitis and a few, small, old renal infarcts. His low clearances were probably the result of these abnormalities plus mild heart failure.

The explanation of lowered clearances in Subject E is not clear unless his age, tertiary syphilis and suppurative skin lesions had combined to decrease his renal function.

The failure of rate of urine flow to affect the per cent of penicillin excreted should discourage attempts to increase the effects of penicillin by dehydration except in cases of susceptible urinary tract infection.

Neither intravenous doses of crystalline penicillin equivalent to 117,000,000 units per day for one hour nor the maintenance of serum levels of 50 to 100 units per cc. in

one subject (G) for sixty days produced toxic effects.

SUMMARY AND CONCLUSIONS

1. Penicillin is excreted by the renal tubules.

2. Clearance values of penicillin are approximately the same as for diodrast.

3. Maximal tubular excretory capacity for penicillin (TM_P) in the normal male is approximately 3,000,000 units (1,800 mg.) per hour, or 50,000 units (30 mg.) per minute.

4. The TM_P and penicillin clearances of certain patients with subacute bacterial endocarditis are decreased and result in supranormal concentration of penicillin in the serum.

5. Rate of urine flow does not affect the rapidity of penicillin excretion.

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Pulmonary Atelectasis in Stuporous States*

A Study of Its Incidence and Mechanism in Sodium Amytal Narcosis

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THE complications of the immobilization which results directly or indirectly from a variety of common illnesses are of general importance. Within recent years attention has deservedly been focused on the frequent and dangerous complications of phlebothrombosis. That restriction of movement has importance in leading to postoperative bronchopneumonia has long been the concern of anesthetists. We believe that a similar or identical mechanism leading to pulmonary complications frequently operates in common medical conditions associated with coma and stupor, and at times, with immobilization in bed without disturbance in consciousness.

Pulmonary atelectasis and related phenomena were observed by the authors during continuous deep sodium amytal narcosis in patients with combat neuroses. In all instances the atelectasis was lobular or segmental and located in one or both lower lung lobes. Usually it was transient. This complication has received scant attention, although bronchopneumonia is frequently found postmortem in patients who succumb to toxic doses of the drug.

Fever is also a common complication of narcosis.[1–4] No cause for this has been shown, although various suggestions including infection and a central effect of the drug have been made. In most instances the urinary tract, nose, throat, sinuses and ears were found normal. Our experiences confirmed these observations. We noted that pulmonary atelectasis was always accompanied by fever, although fever was observed in the absence of demonstrable atelectasis. The present study was undertaken to determine the frequency and character of the pulmonary changes during deep sodium amytal narcosis, their mechanism and their relationship to fever and other phenomena in a group of healthy young adults.

METHOD

Approximately 350 patients were studied in this series which was carried out in a U. S. Army hospital in 1943 to 1944. All were young adult males between the ages of twenty and twenty-eight. They were carefully studied prior to treatment and special ear, nose and throat examinations as well as studies of the lungs were made. No patient was narcotized if evidence of infection was present.

Three hundred of these patients were deeply narcotized by sodium amytal in the following manner:[5] All sodium amytal was administered by mouth and large doses were given only after the patient had been fed. The initial dose for a man weighing 150 pounds was 0.8 Gm. (12 gr.) given at 8 A.M. This was followed two hours later by a second dose of 1.0 Gm. (15 gr.). The patient then slept until about 5 P.M. He was awakened, his mouth, face and hands cleaned and he was taken to the bathroom to void and then was fed. After eating he

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received 1.2 Gm. (18 gr.) of sodium amytal by mouth and was allowed to sleep all night. For the following two days he received 1.4 Gm. (21 gr.) of sodium amytal after breakfast and 1.4 Gm. (21 gr.) after supper. If the required depth of sleep was not obtained by this dosage, additional doses of sodium amytal were given. Often the two main doses had to be either increased or decreased depending upon the weight of the patient and his tolerance to the drug. An average deeply narcotized patient received about 3.0 Gm. (45 gr.) of sodium amytal each day for three days. The patients were fed twice daily, morning and evening, and after each feeding they received their main doses of sodium amytal. They received a minimum of 1,500 cc. of fluid daily in the form of water, fruit juices and milk.

In all patients deep sleep was maintained for forty-eight hours. This necessitated a stay of from sixty to seventy-two hours in the narcosis ward. A patient was considered to be in deep sleep if he did not respond when his blood pressure and temperature were taken, his position changed or when airplanes flew directly overhead. His respirations were shallow and the pupils slightly constricted. He moved sluggishly and only momentarily when the skin was perforated by a pin. He no longer appeared to dream. This depth of sleep was attained twice daily, the middle of the day and the middle of the night. During the morning and evening meals narcosis was relatively light and is referred to as light or drowsy sleep or narcosis. Reference to Figure 7 illustrates a typical three-day period of narcosis. The depth of sleep is indicated at the top of the figure in black. The temperature, pulse, respirations and sodium amytal doses are indicated on the chart.

At the end of three days of narcosis the patients were removed to a recovery ward for one to two days. During the first day of postnarcosis many were still mentally dull, their muscles hypotonic and their breathing shallow. During the second day all became restless and in spite of ataxia moved around a good deal, usually with assistance. They received sedation only at night.

In fifty deeply narcotized patients detailed x-ray studies were made. The x-ray technic was as follows: The day before narcosis was started a chest x-ray at 6 feet target distance was taken, with the patient standing. The purpose of this x-ray was to rule out a pulmonary pathologic condition prior to treatment. During and after narcosis all x-rays were taken with the patient supine in bed. These films were taken once daily at 1 P.M., the time of day when narcosis was uniformly deepest. Following narcosis they were taken at the same time. Additional films were taken when an unusual rise in temperature occurred or whenever otherwise indicated. These films were taken with a portable army field unit at a 30 inch distance with the central ray directed halfway between the manubrial notch and the xiphoid process. Particular care was taken to avoid the slightest rotation of the patient in order that the chest be well centered. The authors were personally responsible for taking these films. All exposures were made during the height of an average inspiration; care was taken to avoid exposures during irregular respirations. Postnarcosis films were taken during quiet respirations to simulate as nearly as possible the conditions of the narcotized patient. The exposure factors for individual patients were always the same to insure uniformity of radiographs.

The following additional studies were made in deeply narcotized patients: (1) Eight patients were fluoroscoped on several occasions with a portable unit in the narcosis room and tracings of the diaphragmatic excursions were made. (2) Respiratory tracings were obtained during the breathing of air and oxygen with a Sanborn Waterless (type 8 MC) basal metabolism machine in

twelve patients. These were utilized to determine the average tidal air in deeply narcotized patients. (3) Samples of arterial blood were withdrawn under oil from the radial artery of eight patients for comparison of their color before and after the breathing of oxygen. This was to determine if the cyanosis of the mucous membranes and nail beds was accompanied by cyanosis of the arterial blood. (4) White blood counts, differentials and sedimentation rates were determined when indicated and the urine was examined daily during narcosis. The Wintrobe method for determining sedimentation rates was employed and 10 mm. was considered the upper limit of normal. (5) In eight patients daily hematocrit determinations were made to rule out dehydration as a cause of fever.

The fifty remaining patients were more lightly narcotized (receiving 2.0 Gm. (30 gr.) of sodium amytal daily). The incidence of fever was determined in these and compared with the incidence of fever in another series of fifty deeply narcotized patients who received an average of 2.9 Gm. (43½ gr.) of sodium amytal daily.

FINDINGS

General Clinical Observations. The following clinical phenomena were observed in narcotized patients: During the induction of narcosis the respirations were shallow and irregular. Sometimes periods of apnea occurred. As the narcosis deepened the breathing became regular with a rate of 18 to 20 per minute but very shallow. The pupils became moderately constricted still reacting to light. A subsequent dilatation of the pupils heralded deeper and alarming narcosis. Muscle tone gradually lessened with a concomitant loss of reflex activity. Analgesia usually developed to a degree that when blood was withdrawn from the radial artery, the patient would either not move or only make an initial weak attempt to withdraw his arm. Loud noises did not disturb patients in deep narcosis and they no longer appeared to dream. Examination of the chest during deep narcosis revealed both diaphragms elevated, breath sounds faint but otherwise normal and no râles. To percussion the chest was normal. Respirations became very shallow and entirely diaphragmatic. The systolic blood pressure usually fell to between 80 and 100 mm. of mercury. In deeply narcotized patients the skin, particularly of the extremities, was cool even when some fever was present.

Narcosis of this depth, referred to as deep sleep or deep narcosis, was attained twice in each twenty-four hours, the middle of the day and middle of the night. In the intervals the narcosis lightened and is referred to as light or drowsy sleep or narcosis. During these latter periods (morning and evening) the patients were toileted, fed and medicated. This twice daily fluctuation of narcosis is emphasized at this point as it will be referred to repeatedly in this paper.

The systolic blood pressure at times fell below 80 mm. of mercury during the period of deep narcosis, at which time oxygen was administered for five to ten minutes. This returned the blood pressure to its former or a higher level promptly and it usually remained there. If necessary, oxygen was administered repeatedly. Mild cyanosis of the nail beds and mucous membranes was observed in most patients. Severe cyanosis was not so common and when present it was usually accompanied by falling blood pressure. This complication was also promptly remedied by the breathing of oxygen. A weak pulse, falling blood pressure, severe cyanosis and dilatation of and reduced reactivity of the pupils to light were the danger signals which were vigilantly looked for. The breathing of oxygen and infusion of intravenous 5 per cent glucose in normal saline constituted the only emergency therapy that was ever necessary for these

complications. An occasional patient was bothered by an excess of mucus. This necessitated the frequent use of oral and pharyngeal suction. Fevers appeared to be more common in these patients but an excess of mucus was by no means the cause of fever in all subjects.

TABLE I
INCIDENCE OF FEVER IN LIGHTLY AND DEEPLY NARCOTIZED PATIENTS

No. Cases	Average Daily Sodium Amytal Intake	Axillary Temperatures Above 90°	Axillary Temperatures Above 101°
50	2.0 grams (30 grains)	24%	6%
50	2.9 grams (43½ grains)	46%	20%

Relation of Body Temperature to Narcosis. Variations in body temperature were observed in most narcotized patients. (All temperatures were taken in the axilla. This temperature was 0.6 to 1.0 degrees lower than mouth temperature in narcotized patients.) During the induction and the first four to eight hours of deep narcosis the body temperature usually fell 1 to 2 degrees. On the second and third days the average temperature rose above the first day level and was usually highest when narcosis was deep. Thus, there was usually a twice daily temperature rise, the high points occurring during the mid-day and midnight. Although an elevated temperature was occasionally recorded on the first day of narcosis, this was unusual. It almost always occurred during the second twelve hours and followed an initial fall in temperature.

A further relationship of fever to the depth of narcosis is shown by the following observations of one hundred patients. (Table I.) In a group of fifty consecutive patients who received an average daily dose of 2.0 Gm. (30 gr.) of sodium amytal, 24 per cent developed an axillary temperature of 99°F. or more on one or more occasions and 6 per cent of them had fevers of 101°F., or above by axilla. A second group of fifty consecutive patients received a larger average dose of sodium amytal (2.9 Gm. daily; 43½ gr.) and their narcosis was accordingly deeper. Forty-six per cent of these developed an axillary temperature of 99°F. or more and in 20 per cent the temperature rose to 101°F. or more. Thus, an increase in the average sodium amytal intake from 2.0 to 2.9 Gm. more than doubled the incidence of fevers.

The foregoing findings appear to confirm the observation that single large doses of sodium amytal cause a definite lowering of the body temperature.[6] With continued narcosis, however, new factors are introduced which cause the temperature to rise in proportion to the degree of narcosis.

Observations on Respirations and Oxygenation of the Arterial Blood. The twice daily temperature and narcosis fluctuations were accompanied by concomitant fluctuations in the tidal air, movements of the diaphragm and oxygenation of the arterial blood. The tidal air in deeply narcotized patients averaged 150 to 300 cc. when breathing oxygen. This is a considerable reduction from a normal of about 550 to 750 cc. for young adult males in good physical condition.* During light narcosis (at or about meal time) it was obvious that respirations had increased in depth but still were shallow. Satisfactory measurements of tidal air could not be obtained, however, because the patients were not cooperative in this state. The rates of respiration were altered very little by narcosis, remaining at or about 18 to 20 per minute. Irregular breathing was common and most marked during the change from light to deep or deep to light narcosis. Short periods of apnea or of slowed-down breathing appeared during these

* Personal communication from Dr. Mandel E. Cohen: Under basal conditions and breathing oxygen the tidal air of normal young men averaged 743 cc. and for others with neurocirculatory asthenia, 553 cc.

TABLE II*

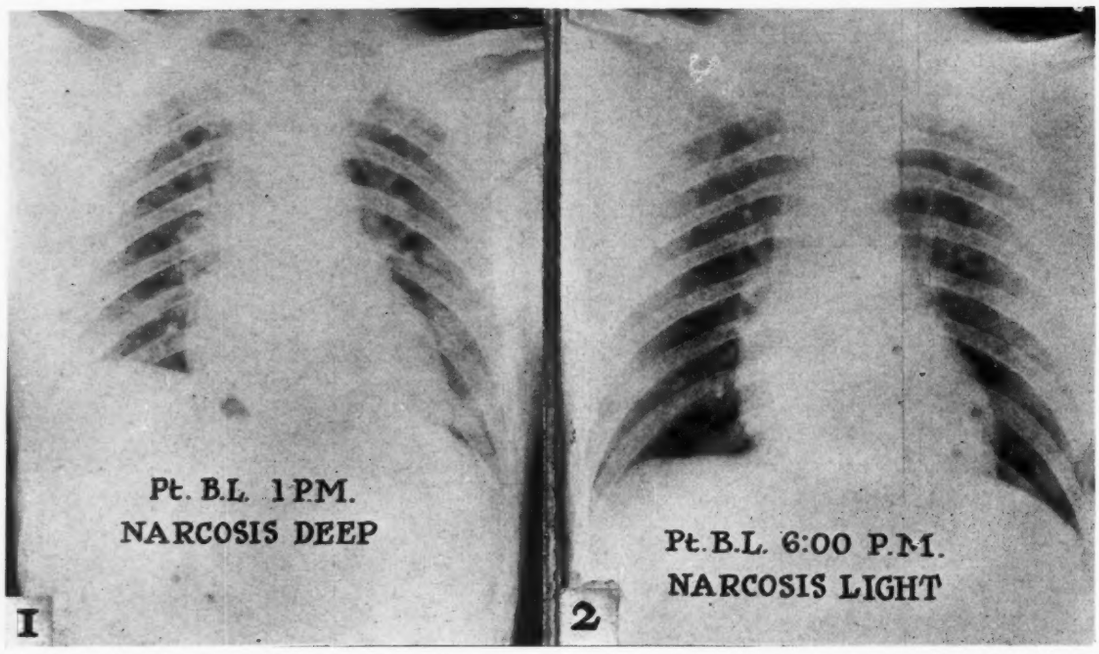
Case	Day	Temperature °F.			Respirations		Sodium Amytal Gm./Day	Elevation of Diaphragm		"Shingling"		Lung Changes	
		Average	High	Low	Average	High		Right	Left	Right	Left	Right	Left
1	1	97.1	98.0	96.4	18–20	22	2.6	++++	++++	+	+	+	+
	2	97.4	98.0	96.4	18–22	24	3.6	++++	++++	+	+	+	+
F. P.	3	97.4	98.0	96.6	18.22	25	4.0	++++	++++	+	+	+	+
	4	.....	.....	....	.....	..	...	++++	+++	+	+	+	+
	5	.....	.....	....	.....	..	...	0	0	0	0	0	0
2	1	97.4	98.4	97.0	16–20	21	2.0	+++	+++	+	+	+	+
A. D. A.	2	98.1	98.6	97.0	18–20	21	1.8	++	++	+	+	+	+
	3	97.0†	.....	....	.....	..	...	++	+	+	+	+	0
3	1	97.0	97.2	97.0	17–20	21	3.8	+++	+++	+	+	+	+
	2	97.6	98.2	97.0	18–22	25	5.0	++++	++++	+	+	+	+
K. I. N.	3	98.0	98.6	97.6	18–20	21	5.2	++++	++++	+	+	+	+
	4	97.6†	.....	....	.....	..	...	+	+	0	0	0	0
	5	.....	.....	....	.....	..	...	0	0	0	0	0	0
4	1	96.9	97.2	96.4	18–20	20	2.2	++	++	±	±	+	+
	2	98.0	98.4	97.6	18–20	21	1.0	+	+	±	±	±	±
D. R. A.	3	98.0	98.8	97.0	18–20	20	1.0	++	++	±	±	+	+
	4	98.0†	.....	....	.....	..	...	+	+	0	0	0	0
5	1	96.8	98.0	96.2	18–20	20	3.6	+++	+++	+	+	+	+
	2	98.4	99.4	98.0	18–20	23	3.0	+++	+++	+	+	+	+
B. U. R.	3	97.0†	.....	....	.....	..	...	+++	+++	+	+	+	+
	4	.....	.....	....	.....	..	...	+	+	0	0	0	0
6	1	97.7	98.2	97.0	18–20	21	3.2	+++	+++	+	+	+	+
	2	98.7	99.2	98.0	18–20	20	2.8	+++	+++	+	+	+	+
K. O. S.	3	98.6	100.0	98.0	18–20	21	2.8	+++	+++	+	+	+	+
	4	.....	.....	....	.....	..	...	0	0	0	0	0	0
7	1	97.3	98.0	96.0	18–20	22	3.2	++++	++++	+	+	+	+
G. A. R.	2	98.1	98.8	97.4	18–20	23	2.8	++++	+++	+	+	+	+
	3	97.9	98.4	97.0	18–20	21	2.8	++++	++++	+	+	+	+
8	1	97.8	99.2	96.6	18–20	22	3.4	+++	+++	+	+	+	+
	2	98.7	99.8	98.0	18–20	20	3.2	++++	++++	+	+	+	+
R. E. F.	3	97.8	99.0	97.0	18–20	20	2.4	++++	++++	+	+	+	+
	4	96.0†	.....	....	.....	..	...	++	+++	0	0	0	0
9	1	98.0	98.6	97.4	18–20	20	3.4	++++	++++	+	+	+	+
M. U. S.	2	98.5	99.4	98.0	18–22	22	2.8	++++	++++	+	+	+	+
	3	98.4	98.8	98.0	18–20	20	...	+++	++++	+	+	+	+
10	1	97.6	98.4	97.2	18–22	22	3.0	+++	+++	+	+	+	+
	2	98.1	99.2	97.0	18–22	24	1.4	+++	++++	+	+	+	+
	3	97.5	98.0	97.2	18–20	22	2.8	+	+	0	0	0	0
P. I. N.	3A	.....	.....	....	.....	..	...	+++	+++	+	+	+	+
	4	97.6	98.0	97.2	18–20	20	4.2	+++	+++	+	+	+	+
	5	98.1	99.4	97.0	18–22	22	2.8	+++	+++	+	+	+	+
	6	97.2†	.....	....	.....	..	...	+++	+++	+	+	+	+
11	1	97.7	98.0	97.4	18–20	21	3.2	++	++	+	+	+	+
	2	97.9	98.6	97.6	20–22	26	3.4	+++	+++	+	+	+	+
P. H. O.	3	98.2	98.8	98.0	20	20	2.4	+++	+++	+	+	++	+
	4	98.0†	.....	....	.....	..	...	+	+	+	+	+	+
12	1	97.3	98.0	96.4	18–20	20	3.0	+++	+++	+	+	+	+
	2	96.9	97.2	96.2	18–20	21	1.6	+++	+++	+	+	+	++
D. A. L.	3	97.9	98.8	97.4	18–20	20	2.0	+++	++++	+	+	+	++
	4	98.0†	.....	....	.....	..	...	0	0	0	0	0	0
13	1	96.8	97.4	96.2	18–20	21	3.0	++++	+++	+	+	++	+
	2	97.5	98.6	96.6	18–21	24	3.0	++++	++	+	+	++	+
W. S.	3	97.2	97.6	97.0	18–20	21	3.8	+++	+++	+	+	+	+
	4	.....	.....	....	.....	..	...	++	+	0	0	+	0
14	1	97.8	97.8	97.6	18–20	22	3.8	+++	+++	+	+	++	+
	2	98.1	98.6	97.6	18–22	24	4.0	++++	++++	+	+	++	+
V. A. N.	3	97.6	98.2	97.2	.....	..	...	++++	+++	+	+	++	+
	4	.....	.....	....	.....	..	...	+++	+++	+	+	+	+
15	1	98.0	99.0	96.2	16–20	20	3.0	++++	++++	+	+	+	++
	2	98.1	99.2	98.0	18–20	20	3.2	+++	+++	+	+	+	++
S. T. A.	3	97.9	99.4	96.4	18–20	20	3.4	+++	+++	+	+	++	+
	4	97.2†	.....	....	.....	..	...	0	0	0	0	0	0
16	1	97.7	98.6	97.0	18–20	21	3.2	++	+++	+	+	+	+
	2	98.2	99.0	97.6	18–22	22	2.8	+++	+++	+	+	+	++
M. A. L.	3	98.8	99.2	98.0	18–22	22	3.4	+++	+++	+	+	+	++
	4	99.0†	.....	....	.....	..	...	+++	+++	+	+	+	++
	5	97.6†	.....	....	.....	..	...	+	+	0	+	0	+
17	1	97.4	98.2	96.6	18–20	20	3.0	+++	+++	±	±	+	+
	2	98.7	99.6	98.0	18–21	21	3.2	+++	++	±	±	++	+
G. R.	3	98.0	99.8	96.0	18–20	20	1.2	0	+	0	0	+	+
	4	96.0†	.....	....	.....	..	...	0	+	0	0	0	+

TABLE II.—(*Continued*)

Case	Day	Temperature °F.			Respirations		Sodium Amytal Gm./Day	Elevation of Diaphragm		"Shingling"		Lung Changes		
		Average	High	Low	Average	High		Right	Left	Right	Left	Right	Left	
18	1	97.5	98.8	96.2	18–20	21	3.0	++++	+++	+	+	++	+	
	2	98.6	99.4	97.4	18–22	28	3.2	++++	+++	+	+	++	+	
S. C. H.	3	98.9	100.2	97.6	18–20	20	...	++++	+++	+	+	++	+	
	4	97.0†	.....	....	.....	..	...	++	+	+	+	0	0	
	5	.....	.....	....	.....	..	...	+	+	+	+	0	0	
19	1	97.6	98.8	96.6	18–20	21	2.2	+++++	++++	++	++	++	+	
	2	99.1	101.0	98.4	20	21	1.0	.....	.....	....	....	.....	.....	Polymorphonuclears 82%
F. E.														Sed. rate 9 mm.
	3	98.2†	.....	....	.....	..	...	+	+	0	0	0	0	
20	1	97.1	97.6	96.6	18–20	20	5.4	++++	++++	+	+	++	+	
	2	99.1	100.0	98.2	18–20	22	4.0	++++	++++	+	+	+	+	WBC 6,250
A. C.														Sed. rate 9 mm.
	2A	.....	.....	....	.....	..	...	++++	++++	+	+	+	+	
	3	99.6	100.0	98.6	18–20	20	4.2	++++	++++	+	+	+	++	
	4	97.0†	.....	....	.....	..	...	0	+	0	0	0	+	
21	1	97.3	98.2	97.0	18–20	22	3.6	++	++++	+	++	+	++	
	2	98.7	100.0	98.0	18–20	20	2.4	+++	++++	+	++	+	++	WBC 10,450; Polymorphonuclears 64%; Sed. rate 8 mm.
R. O. N.														
	2A	.....	.....	....	.....	..	...	+++	++++	+	++	+	+	
	3	.....	.....	....	.....	..	...	+	++	+	+	0	+	
22	1	98.0	100.8	96.0	18–24	26	2.6	+++	++	+	+	++	+	
	2	99.4	100.6	98.0	20–26	28	1.6	+++	++	+	+	++	+	
	3	98.0	98.8	97.0	18–20	20	1.4	+++	+++	+	+	++	+	WBC 9,600; polymorphonuclears 72%; sed. rate 6 mm.
D. U. K.														
	4	98.0†	.....	....	.....	..	...	+++	++	+	+	++	+	
	5	.....	.....	....	.....	..	...	+	0	0	0	+	0	
23	1	97.8	100.4	97.0	18–20	24	3.2	++++	++++	±	±	+	+	WBC 8,250; polymorphonuclears 34%
	1A	.....	.....	....	.....	..	...	++++	++++	±	±	+	++	sed. rate 9 mm.
B. E. R.	2	98.0	99.6	96.2	18–20	20	3.0	++++	++++	±	±	++	++	
	3	99.1	99.8	98.0	18–20	23	2.0	++++	++++	±	±	++	++	
	4	98.8†	.....	....	.....	..	...	+	+	0	0	0	0	
24	1	97.5	98.8	97.0	18–20	21	3.0	++++	++++	+	+	+	+	
	2	98.1	99.0	97.0	18–22	22	3.2	++++	++++	+	+	+	+	
	3	100.5	102.4	99.4	18–22	36	...	+++++	++++	+	+	+	+	WBC 12,000; polymorphonuclears 71%
M. A. U.														
	3A	.....	.....	....	.....	..	...	+++++	++++	+	+	+	++	
	4	98.2†	.....	....	.....	..	...	++++	+++	+	+	+	++	
	5	.....	.....	....	.....	..	...	++	++	+	+	0	++	
25	1	97.5	99.2	96.6	18–22	24	3.0	+++++	+++++	+	+	++	+	
	2	99.1	100.4	98.0	18–22	24	3.2	+++++	++++	+	+	+++	+	WBC 8,650; polymorphonuclears 68%
N. O. T.	3	98.4	99.6	97.8	18–20	21	2.8	+++++	++++	+	+	++	+	
	4	101.0†	.....	....	.....	..	...	+++	+++	+	+	++	+	WBC 16,000
	4A	102.0**	.....	....	.....	..	...	+++	+++	+	+	+	++	
26	1	97.6	98.8	96.4	18–20	21	3.0	+++	+++	+	+	+	+	
	2	99.1	100.6	97.2	18–25	32	2.0	+++	+++	+	+	++	+++	WBC 10,600; polymorphonuclears 68%
	3	97.4	98.2	97.0	18–20	21	3.4	+++	+++	+	+	++	+++	
	3A	.....	.....	....	.....	..	...	+++	+++	+	+	++	+++	
L. E. E.	4	97.8	98.0	97.4	18–20	22	5.0	++++	++++	+	+	++	+++	
	5	98.0	98.8	97.6	18–20	23	2.8	++++	++++	+	+	+	+++	
	6	97.4†	.....	....	.....	..	...	+++	+++	+	+	+	++	
	7	97.0†	.....	....	.....	..	...	+++	+++	±	±	+	+	
	8	.....	.....	....	.....	..	...	++	++	0	0	+	+	
27	1	97.3	98.6	97.0	18–24	30	2.4							
	2	99.4	101.4	97.8	20–30	37	2.4	+++	+++	+	+	+++	+	
R. A. V.	3	98.0	98.8	97.4	20–30	33	2.8	+++	+++	+	+	+++	++	
	4	97.6†	.....	....	.....	..	...	+	+	0	0	+++	+	
	5	.....	.....	....	.....	..	...	0	0	0	0	++	0	
28	1	97.4	97.4	97.4	18–20	21	3.0	+++	++	+	+	+	+	
	2	98.6	99.6	97.4	18–21	21	2.8	+++	++	+	+	+	+	
	3	100.6	103.0	98.0	18–28	29	1.4	++++	++	++	+	++	+	
G. H.	3A	.....	.....	....	.....	..	...	+++	+++	+	+	+++	++	WBC 10,800; polymorphonuclears 74%; sed. rate 16 mm.
	4	98.0†	.....	....	.....	..	...	++	++	+	+	++	++	
	5	.....	.....	....	.....	..	...	++	+++	0	0	±	±	

* Contains the essential data on each of the twenty-eight carefully studied patients. All temperatures were taken in the axilla. With reference to elevation of the diaphragm, "+" indicates a rib or interspace, "++" a rib plus an interspace, etc. "Shingling" signifies a collapse of the chest cage; "+" indicates marked narrowing of the interspaces and "++" indicates an actual overlapping of the ribs. In the column lung changes "+" indicates generalized decreased aeration, "++" indicates small focal densities and "+++" moderately large focal densities. (Fig. 16.) In the column labeled remarks, white blood counts and sedimentation rates are recorded. In the temperature and respiration columns, "average" indicates actual averages for twenty-four hours, "high" indicates the single high reading and "low" indicates the single low reading. The total dose of sodium amytal per day is listed in grams.

† Single temperature, 10 A. M. ** Temperature dropped to 98.6°F. by mouth in four hours.



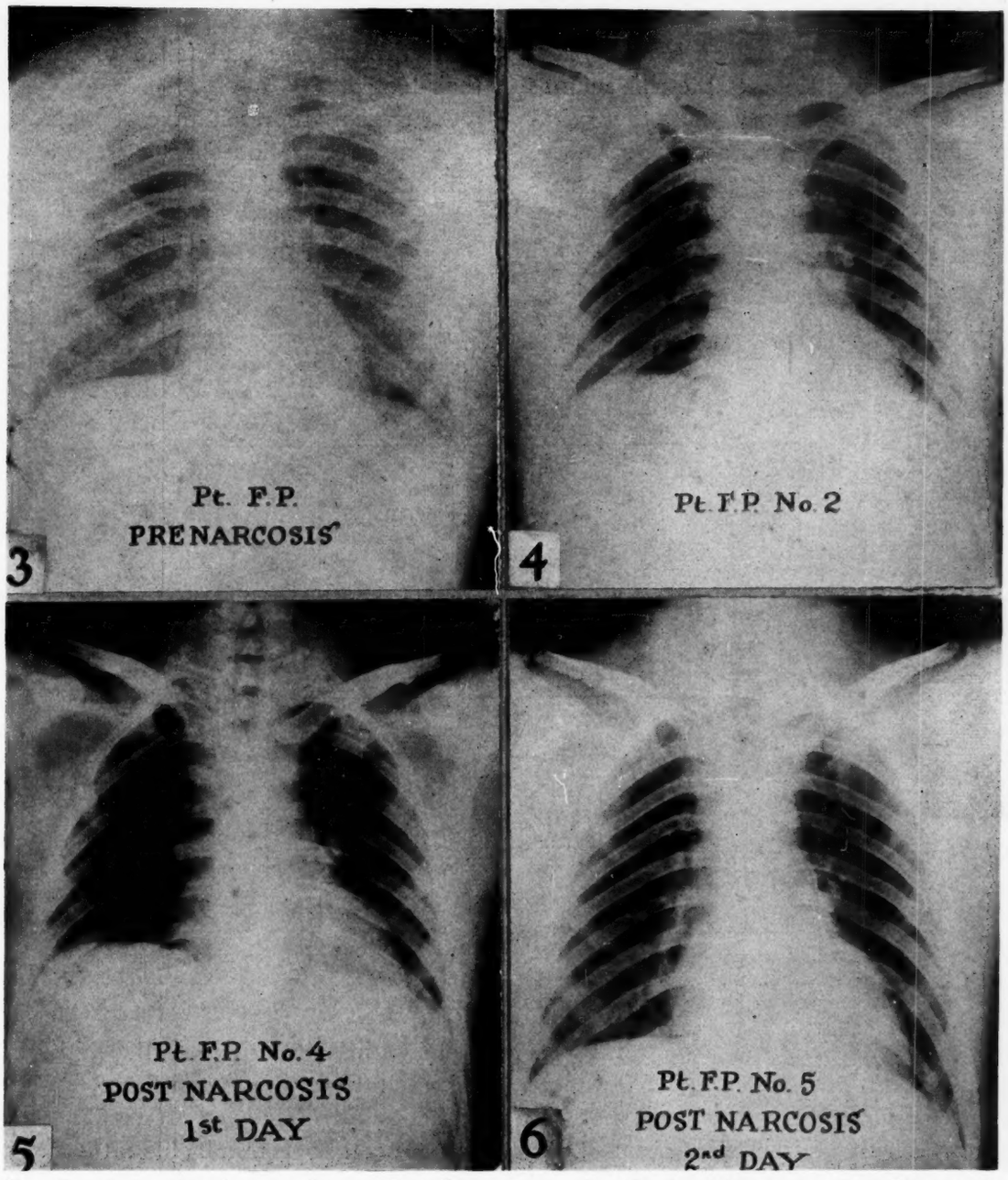
FIGS. 1 and 2. Figures 1 and 2 are x-rays of the same patient. Figure 1 illustrates the decreased aeration of the lungs, collapsed chest and elevated diaphragm which accompanied deep narcosis. Figure 2 was taken five hours later when the narcosis was lighter and the patient could be fed. Note the increased aeration of the lungs, depression of the diaphragm and widening of the rib interspaces.

transition periods. During deep narcosis respirations were usually regular.

Moderate rises in temperature (100 to 101°F.) failed to alter either the rate or character of respirations. Higher temperatures, however, were accompanied by significant increases in the respiratory rate and by restlessness. (Table II; cases 22, 26, 27 and 28.) In these patients focal as well as general pulmonary changes were present.

The diaphragms became progressively more elevated and the chest more collapsed as the narcosis deepened. This was accompanied by a corresponding decrease in aeration of both lungs. Figures 1 and 2 illustrate these changes in one patient during deep and light narcosis. These two films were taken five hours apart. Diaphragmatic excursions were also decreased during narcosis. In deeply narcotized patients the excursions of the diaphragm were observed by fluoroscopy to vary between 0.5 and 2.0 cm. and averaged 1.0 cm. This constitutes a marked reduction from a normal of about 3.0 cm. in the average supine young male during quiet respirations.

Cyanosis of the finger nails and mucous membranes was observed in nearly every deeply narcotized patient. This was occasionally severe. In all instances the breathing of oxygen restored these structures to a normal color. It is of some interest that an increase in the depth of respirations, to be discussed later, occurred after the cyanosis had disappeared, suggesting that the increased depth of respirations resulted from, rather than caused, the improved oxygenation of the blood. In eight cyanotic patients arterial blood, drawn under oil from the radial artery, was tinted slightly blue. A second sample of arterial blood obtained in the same way from the same artery by a separate puncture showed that this cyanosis of arterial blood disappeared after oxygen had been assimilated for five to ten minutes. Cyanosis of the mucosa and nail beds had also disappeared.



FIGS. 3 to 6. A series of x-rays of one patient. Figure 3 was taken the day prior to narcosis and is normal. Figure 4 was taken on the second day of narcosis and shows a high diaphragm, slightly collapsed chest and slightly decreased aeration of the lungs. Figure 5 was taken one day after the end of narcosis and shows little change from Figure 4. In Figure 6 greatly increased aeration of the lungs is evident.

Serial X-ray Studies of the Lungs during Narcosis. Fifty patients were studied by daily x-rays taken at mid-day when narcosis was deepest. In twenty-eight patients these studies were complete and technically satisfactory in all respects and are summarized in Table II. In this table the cases are arranged in order of increasing severity of their pulmonary changes. The first ten cases in this table exhibited only the basic changes characteristic of deep narcosis alluded to before. These are (1) symmetrical elevation of the diaphragms; (2) collapse of the chest cage and (3) decreased aeration

of the lungs. By collapse of the chest is meant a narrowing of the rib interspaces and an increasing slope of the ribs such as one sees in the expiratory phase of respiration. It has already been shown that these basic changes vary with the depth of narcosis. Figures 3, 4, 5 and 6 show a representative series of x-rays from one of these patients. The prenarcosis film is normal. (Fig. 3.) Figure 4 is characteristic of the narcosis period and was taken on the second day of narcosis. The diaphragms are elevated bilaterally to just below the third rib on the right and the top of the fourth rib on the left anteriorly. The chest cage is collapsed. The lung fields are poorly aerated but otherwise not remarkable. On the first day postnarcosis (Fig. 5) there is only a slight increase in the aeration of the lungs. On the second postnarcosis day (Fig. 6) the chest is normally aerated. On the first postnarcosis day many patients were still quite drowsy and had failed to reexpand their lungs.

A typical representative temperature, pulse and respiration chart for the ten patients showing only these basic lung changes is shown in Figure 7. Note the initial drop in temperature on the first day followed by higher temperatures on the second and third days. It can be seen in Table II that most of the cases in this group had an elevated body temperature at some time during narcosis. The degree of this elevation was significant in several patients and was highest during deep narcosis. Respiratory changes did not accompany fever in these patients.

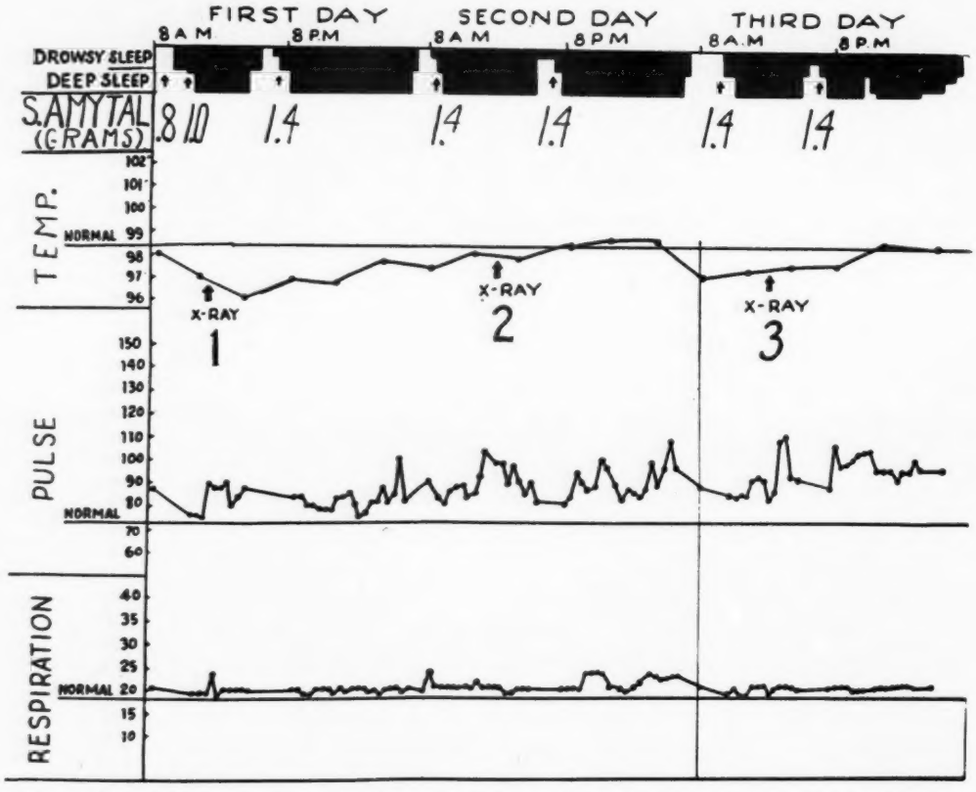
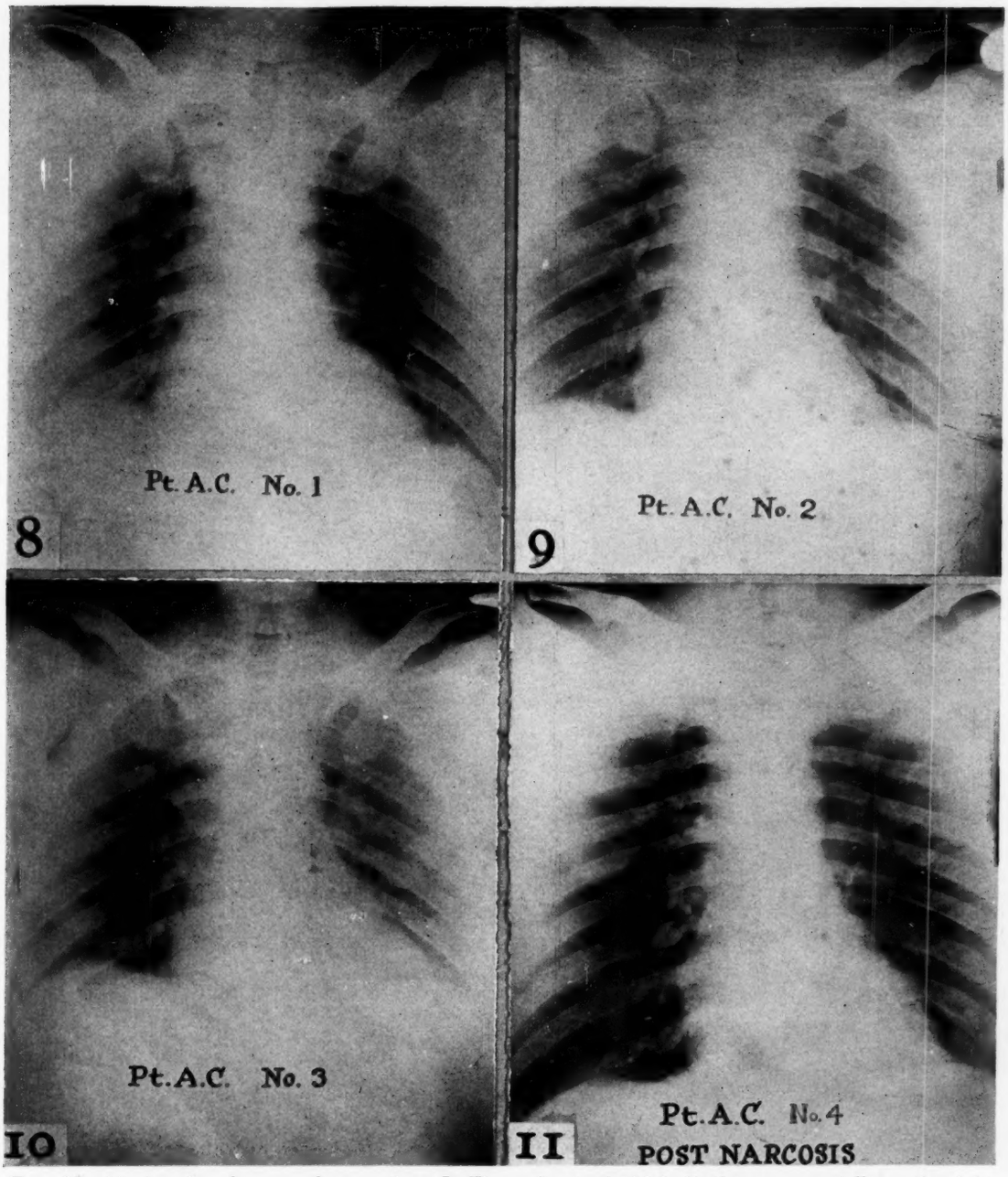


FIG. 7. A typical temperature chart for one of the patients showing only decreased pulmonary aeration. Note the initial drop in temperature. On the second and third days the general level of body temperature is much higher. The arrows indicate when the x-rays were taken.

The remaining eighteen patients presented further pulmonary changes consisting of (1) asymmetrical elevation of the diaphragm, (2) patchy, irregular densities in the lung fields and (3) minimal changes



FIGS. 8 to 11. A series of x-rays of one patient. In Figure 8 note the high diaphragm, especially on the right, and haziness at the right lung base. This was taken on the first day of narcosis. Figure 9 shows the lungs on the second day of narcosis. There is considerable clearing at the right base. On the following day (Fig. 10) there is haziness at the left base. In Figure 11, which was taken one day postnarcosis, there is marked clearing of both bases. There is still some cloudiness at the left base and slight elevation of the left diaphragm.

in the symmetry of the chest cage. This latter observation was very difficult to evaluate and is probably of the least practical importance because of the difficulty in positioning the patient for x-ray studies; the slightest rotation of the patient produces an asymmetry of the chest on x-ray films.

In fourteen of these patients the pulmonary changes disappeared or markedly diminished in a few to twenty-four hours. Sometimes patches of atelectasis cleared in one lung only to reappear later in the other. Sometimes the densities were so minimal that their nature could be interpreted only

by comparing films taken on successive days. Figures 8, 9, 10 and 11 illustrate these findings. Figure 8 shows the chest during the first day of narcosis. Note the unusual elevation of the right leaf of the diaphragm and the cloudy irregular density at the right base. Figure 9 is on the second day of narcosis. Note that the right diaphragm has come down and the right base is clear. Figure 10 is on the third day of narcosis and shows haziness throughout the left lung field with definite narrowing of the rib interspaces. Figure 11 is one day postnarcosis. The right lung field is clear, the left diaphragm is still slightly high and the aeration of the lung base although improved is not normal.

The temperature chart for this patient is shown in Figure 12. The low temperature of the first twelve hours is followed by its progressive elevation. The difference between the temperature in these and the preceding ten patients is one of degree only and no grouping of the cases on the basis of temperature alone is possible. A significant increase in the respiratory rate during atelectasis was noted in only one patient in this group. (Table II, case 22.)

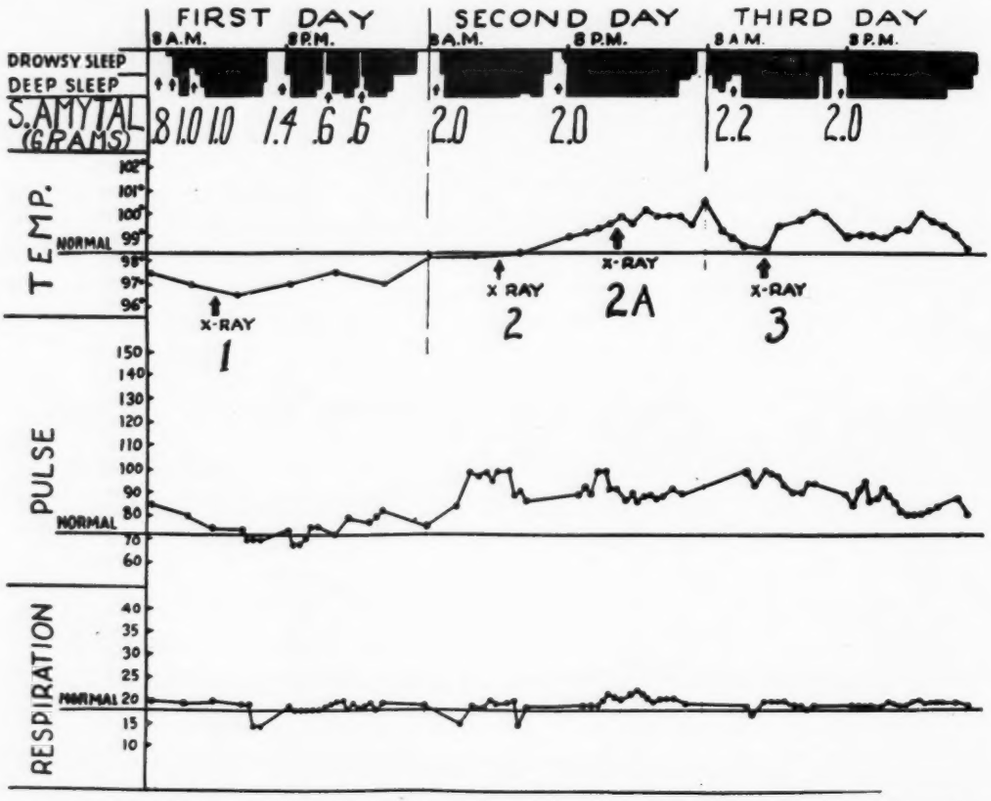
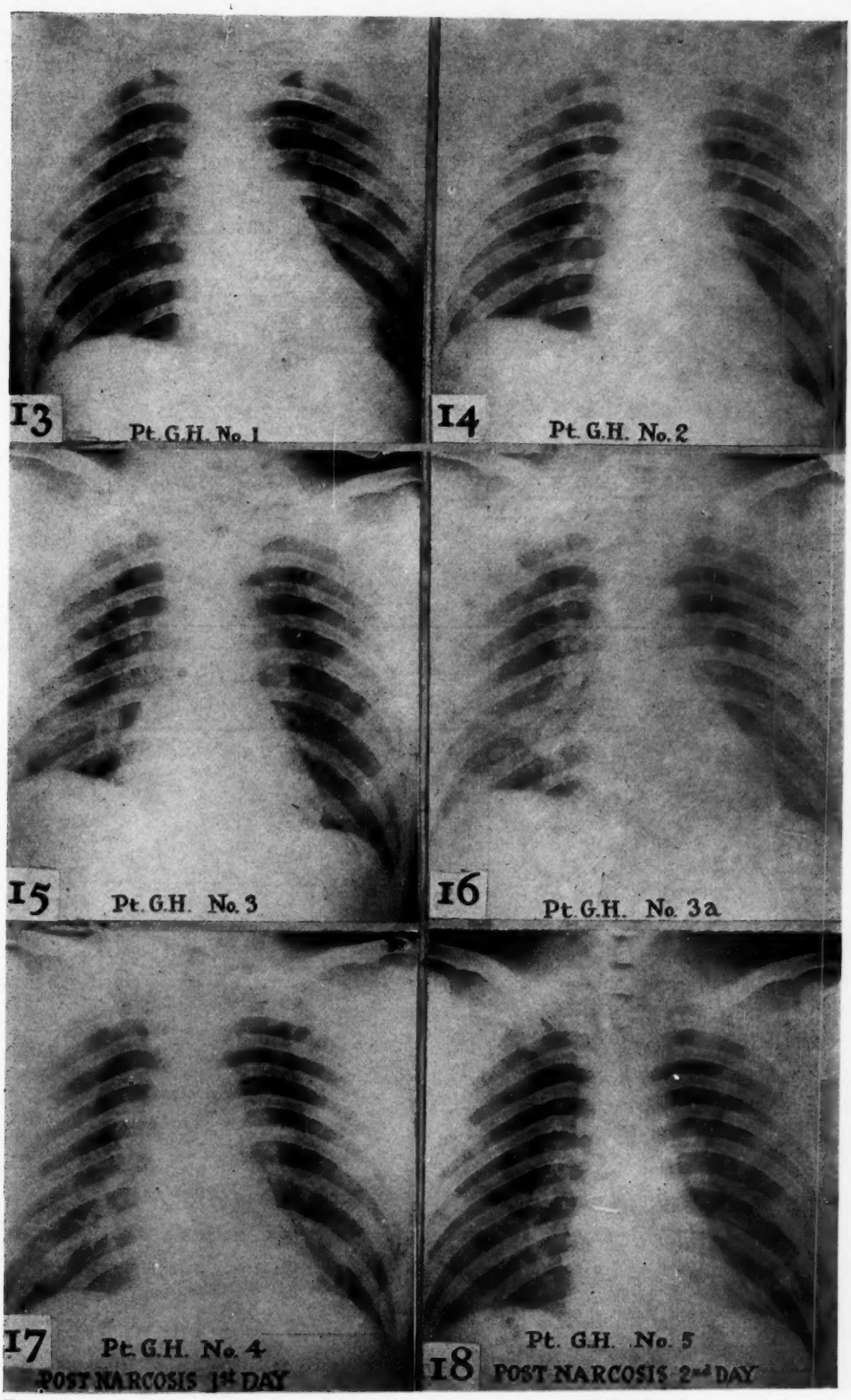


FIG. 12. Temperature chart of the patient illustrated in Figures 8 to 11. The arrows indicate the time that x-rays were taken.

In the remaining four patients the pulmonary changes were more marked and the fever was higher. In two patients the atelectasis disappeared in forty-eight hours and in the remaining two it persisted for four and six days after narcosis. During the bouts of atelectasis three of these patients had significant increases in the respiratory rates and were very restless. Figures 13, 14, 15, 16, 17 and 18 are a series of x-rays from one of these patients. The prenarcosis film (not illustrated) was normal. Figure 13 taken on the first day of narcosis shows no gross change. The lung fields are well aerated. Figure 14, second day of narcosis, shows an elevated right diaphragm with the lung fields less



FIGS. 13 to 18. A series of x-rays of one patient. Figure 13 was taken on the second day of narcosis. Note the elevated right diaphragm and beginning cloudiness extending out from the right hilus. Figure 15 was taken the third day of narcosis. The right diaphragm is still high and the density in the right lower lung field has increased. In Figure 16, taken later on the same day as Figure 15 (Fig. 19), further cloudiness in the area of the right middle lobe is evident. Also the diaphragm is elevated on the left and the left lower lung lobe is cloudy. There is some clearing in both lungs in Figure 17 taken one day after termination of narcosis. In Figure 18, taken on the second day postnarcosis, both lungs are clear and the diaphragm is in normal position.

well aerated than on the first day. Figure 15, taken on the third day, shows bilaterally diminished aeration, persisting elevation of the right diaphragm and a cloudy density in the right lower lung field. Figure 16, taken the evening of the third day of

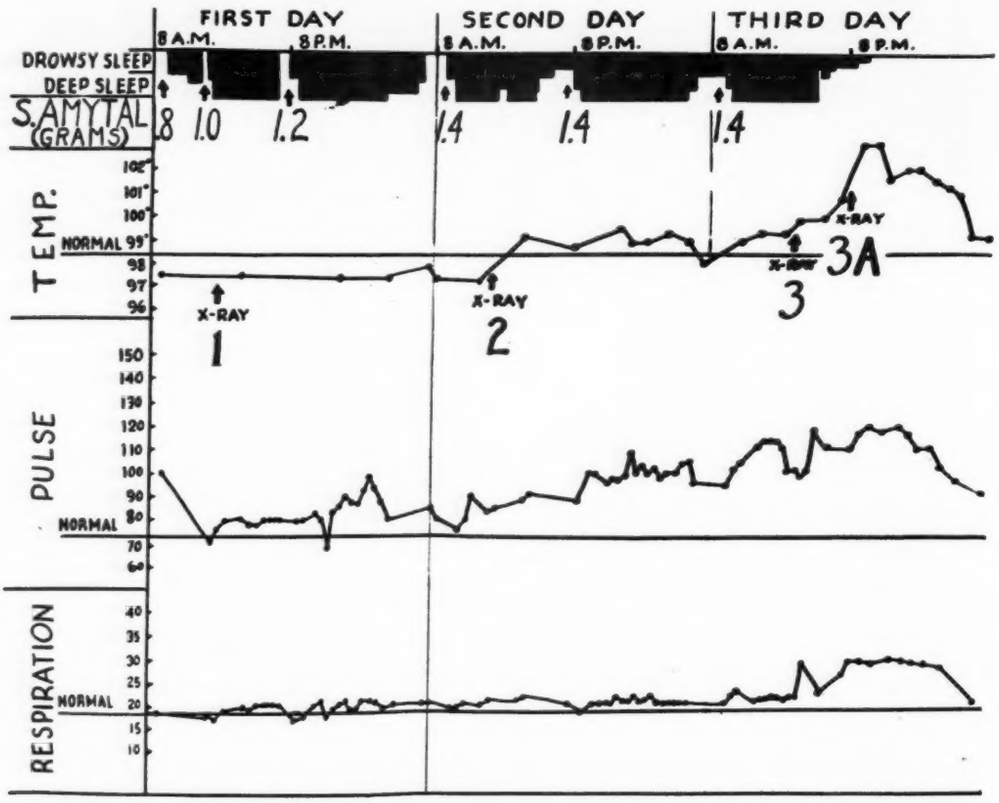


FIG. 19. The temperature chart of the patient illustrated in Figures 13 to 18. The arrows indicate when the x-rays were taken.

narcosis, shows that the density in the right lower lung field has increased and lies in the area occupied by the right middle lobe. The lung fields bilaterally show still further decrease in aeration. Figure 17, taken on the first postnarcosis day the day after Figure 16 was taken, shows the density in the right middle lobe gone and the diaphragm lower. The aeration is improved more on the left than on the right side. Figure 18 was made on the second postnarcosis day. Both lung fields are clear and well aerated.

The temperature, pulse and respiration chart for this patient (Fig. 19) shows the fever and increased respiratory rate which attended the pulmonary changes. The general temperature level was higher in this group of four patients than in either of the two preceding groups. Also, the respiratory rates of three of the patients increased significantly during the atelectasis. (Figure 19, table II, cases 26, 27 and 28.)

Observations on the Urine, Blood and Hydration. Daily urine tests were usually normal. Albumin, red blood cells, white blood cells or casts were very rarely present. Also, the specific gravity of the urine usually ranged between 1.010 and 1.015. White blood cell counts and sedimentation rates were determined in a number of patients with fevers. Some of these are to be seen in Table II. In only one patient (Case 28) was the sedimentation rate greater than normal and the slight increases in leukocytes were not impressive. In occasional blood studies on the patients not included in Table II no greater changes were observed. Detectable concentrations of the blood were shown to

be absent by daily hematocrit determinations in eight narcotized patients who received 1,500 cc. of fluid daily in addition to their regular diet. This is considered to rule out dehydration as a cause of fever in our patients, since with rare exception all patients received 1,500 cc. or more fluid daily.

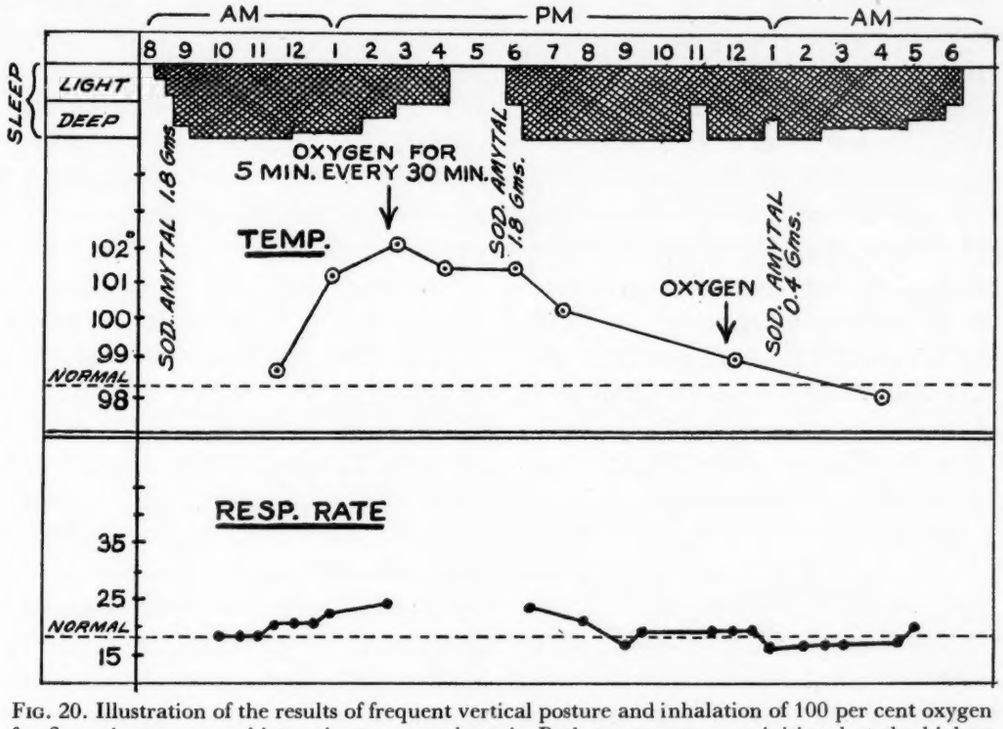


FIG. 20. Illustration of the results of frequent vertical posture and inhalation of 100 per cent oxygen for five minutes every thirty minutes on atelectasis. Both treatments were initiated at the highest point of the temperature at the first arrow and discontinued at the second arrow. Note that the narcosis treatment was not interrupted.

Treatment of Atelectasis in Narcotized Patients. The usual precautions were taken to prevent the development of atelectasis. The patients were turned frequently and fed cautiously. Also, all patients were "walked" supported by several assistants to the toilet to void several times daily and nightly. It was our impression that this procedure very effectively reduced the incidence of atelectasis.

It was also found that the breathing of 100 per cent oxygen increased the depth of breathing of deeply narcotized and cyanotic patients. The oxygen was usually administered with a Boothby rebreathing type of mask. It was found, however, that an equal increase in the depth of respirations occurred when the rebreathing bag was removed from the mask or when the oxygen was furnished from a basal metabolic machine and the expired carbon dioxide was absorbed by soda lime. Furthermore, the addition of 5 per cent carbon dioxide to the oxygen or rebreathing to allow carbon dioxide to accumulate, did not stimulate respirations more than the breathing of oxygen alone in our deeply narcotized cyanotic patients. It should be mentioned that an increase in respirations was observed to follow disappearance of the cyanosis rather than precede it.

These same procedures were used to re-expand the lungs after atelectasis had developed. Patients were given oxygen to breathe for five minutes every thirty minutes or continuously and were held vertically for five minutes every thirty to sixty minutes. Figure 20 illustrates a fall in fever

which occurred in one patient after all of these procedures were used. Since such falls in fever have also been observed spontaneously, one cannot be certain that a cause-and-effect relationship existed in this instance. The results of many such experiences, however, indicate a very favorable effect of these maneuvers upon atelectasis in narcotized patients.

In a number of patients 5 per cent carbon dioxide plus 95 per cent oxygen was administered for five minutes every thirty minutes with the Boothby rebreathing mask. This increased the secretion of mucus to the point that the mouth and pharynx needed to be suctioned frequently to keep the airways free. Fevers appeared to be more frequent in these than in other patients. This point was not controlled statistically. It should be noted that the breathing of oxygen alone was not attended by an excess of mucus.

COMMENTS

Two types of pulmonary changes were observed during deep sodium amytal narcosis. First, all patients exhibited a generalized and uniform decrease in aeration of the lungs, accompanied by symmetrical elevation of the diaphragm and collapse of the chest cage. Second, many patients (eighteen of twenty-eight patients carefully studied) also exhibited focal pulmonary changes of variable appearance, accompanied by asymmetrical collapse of the chest and asymmetrical elevation of the diaphragm. Some focal lesions showed up in x-ray films as irregular hazy densities, some as linear shadows and one occupied the middle lobe and resembled pneumonia. Except for the very transient character of these lesions, they could easily have been confused with atypical pneumonia, which was observed frequently in troops in that area. Fever was present at one time or another in nearly all patients but as a rule the temperatures were higher in patients with both focal and general lung changes.

All pulmonary changes were relatively transient. The focal lesions usually disappeared in a few to twenty-four hours but in two patients the lesions remained after narcosis for two and four days, respectively. They were also observed to shift from one lung to another, possibly as the result of posture. These facts, plus the asymmetrical changes in the diaphragms and chest wall and the absence of indications of infection, are compatible with atelectasis of a lobular or segmental variety.

Our observations suggest that the changes leading to this atelectasis developed according to a definite pattern. Decreased aeration of the lungs was the first detectable change. It appeared to be due to a uniform compression of lung tissue by the collapsed chest and high diaphragm. Possibly some vascular stasis or congestion contributed to this picture of generalized increased density since a high diaphragm alone may not produce it. In a few instances a slight asymmetrical elevation of one half of the diaphragm was observed without detectable pulmonary changes. Perhaps focal changes were present in these patients but were not seen because they were slight or because they were obscured by other structures. Gross focal pulmonary lesions developed next, signifying complete or nearly complete collapse of one or more pulmonary segments. This was observed in about 65 per cent of the carefully studied patients.

The mechanism of massive collapse of one or more pulmonary lobes, following obstruction of their main lobe bronchi by foreign bodies or mucus plugs, is not difficult to demonstrate. In animals such an obstruction internally by a foreign body [7,8] or externally by ligature[8,9] is followed by absorption of all the air from the obstructed lung tissue in from two to twenty-four hours. Some of the gas may be removed as the result of ciliary

action when the bronchus is plugged by mucus[10] but most or all of the air is probably removed by way of the blood stream. If the obstruction is incomplete a ball-valve opening may cause emphysema instead of atelectasis.[8]

The mechanism of the development of lobular atelectasis is less clear. Experimentally, Van Allen[11–13] has shown that obstruction of secondary and smaller bronchi and bronchioles does not cause collapse of lung tissue as long as air passes freely to any portion of the involved lung lobe. In all probability this is due to a free passage of air between adjacent alveoli by way of small anatomical ostia.[14] This exchange of air between adjacent normally aerated and obstructed lung lobules may be sufficient to prevent collapse of otherwise isolated alveoli in the dog.

In view of Van Allen's findings, one would not expect atelectasis to follow simple obstruction of a few small bronchi and bronchioles. It is apparent that factors other than obstruction must be present or that lobular atelectasis is produced by other mechanisms. Compression by a pneumothorax can produce atelectasis. Also, areas of atelectasis have been produced experimentally in emphysematous lungs by pressure of the vertebral bodies on over-riding lung tissue.[8] In this latter instance the atelectasis was confined to the compressed areas. In our deeply narcotized patients the atelectasis was usually in the midlung tissue; there were no lesions confined to the surface to suggest that pressure alone had been their cause.

It is believed that the atelectasis which develops during deep narcosis is not due to compression alone. However, it is clear that the elevation of and reduced excursion of the diaphragm, together with collapse of the chest, are prime factors in its development. First, in deep narcosis the lungs are reduced in volume to a degree commensurate with extreme expiration. A similar although probably smaller decrease in lung volume is present postoperatively.[15] In the expiratory phase of respiration the bronchi and larger bronchioles are reduced in diameter[16] and consequently can be easily obstructed. Furthermore, the processes which keep the air passages patent are interfered with and mucus accumulates. The ciliary action is less effective than normal; a smaller and weaker stream of air passes through the air ways; coughing is absent or ineffective.[17] Second, this partial "collapse" of the lung interferes with the collateral exchange of air between adjacent lung lobules, to the extent that absorption of air by the blood exceeds its entry into blocked alveoli from adjacent normal alveoli. Van Allen found that atelectasis occurred after the occlusion of bronchioles and smaller bronchi if the breathing was forced or difficult, either from stenosis of the trachea or for other reasons. It failed to develop, however, when the breathing was free. Probably the small interalveolar ostia are reduced in size or even obstructed by a reduction in the volume of the lungs much as the airways are reduced in diameter. This is suggested by the fact that these interalveoli ostia are much easier to demonstrate microscopically in expanded than in collapsed lung tissue.[14]

Another factor of debatable and possible of great importance is anoxia. Drinker and his collaborators[18] have shown that the flow of lymph from the lungs of dogs is increased by anoxia. This indicates that there is an excess of fluid in the respiratory bronchioles and distalward. Practically all of our narcotized patients exhibited varying degrees of cyanosis of mucous membranes and nail beds which could be readily changed to normal by the breathing of oxygen. Quite possibly this anoxia increased the amount of fluid in the smaller airways and contributed to their obstruction. The inclusion of carbon dioxide with oxygen in breathing mixtures

when rebreathing types of masks were used apparently caused even a greater outpouring of mucus, much of which appeared in the larger airways and was removed by suction. This is in accord with other experiments of Drinker and his collaborators which demonstrated that the flow of lymph from the lungs of dogs was greatly increased by elevation of the concentration of carbon dioxide in the breathing mixture above normal levels.* Anoxia also appeared to be a factor in maintaining a depression of respiration in our patients. This is suggested by the fact that the breathing of oxygen for three to ten minutes resulted in an increase in the depth of breathing which was usually not sustained after the oxygen had been discontinued.

Lobular atelectasis, often transient, develops in a variety of conditions, in all of which the volume of the lungs and the ventilation are significantly diminished. Pasteur[19] seems to have first called attention to this in diphtheria. He noted collapse of the lower lobes of the lungs in fifteen of thirty-four severely paralyzed diphtheria patients. He made the diagnosis clinically by the presence of (1) increased movements of the lower ribs, (2) reversed movements of the epigastrium during respiration and (3) altered character of the voice and cough. He attributed this atelectasis to paralysis of respiration which allowed the lungs to collapse as the result of their normal elasticity. Pulmonary complications have been observed frequently in acute infectious polyneuritis[20] and in acute poliomyelitis.[21] In both instances hypoventilation due to paralysis appears to have been the important factor. Briscoe[22,23] noted atelectasis in a variety of conditions in which breathing was diminished, either due to paralysis of the muscles of respiration or generalized debility. Linear opacities, which often disappeared after deep breathing, were described by Fleischner[24,25] and were later confirmed.[26] These were thought to be due to shallow breathing from pain, as the result of inflammation near the diaphragm or by generalized debility. In three patients the atelectasis was verified histologically. One wonders how frequently atelectasis is the forerunner of terminal pneumonia when the diaphragms are elevated and restricted in movement by ascites or other abdominal masses. It is not unlikely that it precedes pneumonia in paralyzed and debilitated individuals far more frequently than is recognized.

Transient lobular atelectasis has been noted postoperatively.[27–32] The very marked depression of respiration in deep narcosis with reduced tidal air and vital capacity, collapsed chest and high diaphragm are changes which are also present postoperatively.[33–39] Thus, in operations for the repair of inguinal hernia, the incidence of atelectasis has been reported to be roughly 3 per cent; after general abdominal operations 14 per cent and after gastric and duodenal operations approximately 42 per cent[29,30] The reduction in pulmonary ventilation after operations outside of, or in the lower part of the abdomen or in the chest, is usually about 50 per cent. After upper abdominal operations, however, the reduction in ventilation is even more and has been reported as great as 78 per cent.[34] It is of interest to note that atelectasis has occurred twice as frequently after local or spinal anesthesia as after general anesthesia when given for herniorrhaphy.[30]

Re-expansion of the lungs and aeration of the collapsed alveoli has been attempted in a variety of ways depending upon circumstances. When the condition persists a respirator of the Drinker type is probably

* Recent experiments in sodium amytal narcotized dogs have shown that the fall in arterial oxygen saturation is accompanied by a parallel increase in the carbon dioxide content of the arterial blood. This may have been a more important factor in producing an excess of fluid in the pulmonary airways than anoxia.

of greatest usefulness. Smith[40] believed that reduced vital capacity in poliomyelitis was an indication for the use of a respirator of this type. He stated that the ability to breathe was not sufficient indication to remove a patient from the respirator, but that the patient must also be able to cough effectively. Cooperstock[21] has also warned about the too early removal of patients from the respirator. Zollinger[38] has attempted to increase the vital capacity in postoperative patients by injecting the intercostal nerves which supply the operative field with prolonged anesthetic agents. This procedure appeared to increase the vital capacity and he thought that it decreased the incidence of pulmonary complications. We have employed the same basic principles of treatment; namely, an attempt to reexpand the lungs. The most potent of our procedures was postural and consisted of holding the patient in a vertical position for periods of five to ten minutes. The effect of vertical posture in increasing inspiration has been shown by a recent study.[1] In comatose[4] patients a fairly satisfactory tidal air and adequate pulmonary ventilation can be obtained by the Eve tilt method of artificial respiration. At best, such methods are temporary expedients and can only be useful when the mechanisms producing collapse will be dissipated or lessened in a few hours.

Our second procedure consisted in the breathing of oxygen periodically. This was followed by a gradual increase in the depth of breathing, even when carbon dioxide was not included or was not allowed to accumulate in the breathing mixture. No greater increase in ventilation was obtained by the addition of carbon dioxide to the mixture. Henderson[42] has pointed out the unusual and variable responses of barbiturate narcotized patients and animals to the breathing of oxygen and carbon dioxide-oxygen mixtures.[43] Our experiences are in accord with these observations. A further discussion of the mechanisms involved are, however, beyond the scope of this paper. Intravenous glucose solutions were occasionally helpful, in that they lightened narcosis and in this indirect way increased the depth of breathing.

The mechanism of the fever that accompanies reduced aeration of the lungs with or without atelectasis is not clear. The absence of leukocytosis and the presence of normal sedimentation rates render infection unlikely. Another physiologic mechanism is suggested by the clinical findings of hypoventilation, cold skin and low blood pressure; namely, a lessened heat loss, first from the lungs as a result of hypoventilation and second, from the surface of the body as a result of peripheral vascular collapse. Such a mechanism could result from central depression by the sodium amytal. The twice daily and concomitant fluctuations in the depth of narcosis, fever, hypoventilation and tendency to low blood pressure favor such an explanation.

SUMMARY AND CONCLUSIONS

A group of patients with combat exhaustion, who were being treated with continuous sodium amytal narcosis, exhibited uniform decreased aeration of the lungs accompanied by symmetrical elevation of the diaphragm, collapse of the chest, reduced tidal air and cyanosis. Approximately 65 per cent of these patients also showed transient patchy and irregular densites in the lungs, accompanied by asymmetrical elevation of the diaphragm and slight asymmetry of the chest cage. The focal lung changes were interpreted as atelectasis.

During the first twelve hours of deep narcosis the body temperature usually fell 1 to 2 degrees Fahrenheit. Subsequently, it rose and was higher on the second and third than on the first day. In patients with focal, as well as general lung changes, the fever was usually higher than in those

exhibiting decreased aeration alone. Significant changes in respirations during fever occurred in only a few patients with marked pulmonary lesions. There was a direct correlation between the degree and frequency of fever and depth of narcosis.

The mechanism of the pulmonary changes appears to be, first, compression of lung tissue due to a collapsed chest and high diaphragm; this decreases the diameter of the smaller airways and probably lessens or stops the collateral circulation of air from one to another alveolus by way of the interalveolar ostia. Second, the smaller airways become blocked and lobular atelectasis develops. Anoxia and hypercapnia contribute to this by increasing the fluid content of the smaller airways.

The mechanism of the fever is probably not infectious. It is suggested that a failure of heat loss through the lungs as a result of hypoventilation and from the skin as the result of cutaneous vascular insufficiency is one factor in the production of fever in these patients. The deeply narcotized and cyanotic patients usually exhibited an increased depth of respirations when given 100 per cent oxygen to breathe. This was preceded by a clearing of the cyanosis. The presence of carbon dioxide (5 per cent) in the breathing mixture or its accumulation as the result of rebreathing did not stimulate respirations more than the breathing of oxygen alone.

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Prognosis in Gastric Cancer*

A Study of Five-year Survivors

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In a series of 466 patients with gastric cancer admitted to the University Clinics from 1927 to 1944, 389 (83.5 per cent) underwent operation, 203 (43.5 per cent) being subjected to resection of various types; 150 (32.8 per cent) survived resection.[1] Of the total 466, 377 were seen in the years from 1927 to 1941 and hence were suitable for a study of subsequent course; of these 155 (41.1 per cent) underwent resection and 115 survived. The purpose of this paper is to report a further study of the factors responsible for prolonged survival.

Detailed follow-up was made in 93 (80.8 per cent) of the 115 survivors. Sixty-five (56.8 per cent) were found to have died; twenty-eight during the first postoperative year, twenty-four in the second, seven in the third, five in the fourth and one in the fifth. Twenty-eight patients, constituting 7.4 per cent of the 377, 24 per cent of the 115 or 30 per cent of the ninety-three, survived five years or longer. Walters, Gray and Priestly[2] found 28.9 per cent of 2,322 resection survivors to live five years or more after operation, Custer[3] 27 per cent, Livingston and Pack[4] 25 per cent and Weese[5] 19 per cent. Thus, the five-year survival rate of the patients successfully withstanding gastrectomy for gastric cancer varies from 19 to 30 per cent. In Weese's group this constituted 7.59 per cent of all patients, whereas in Oughterson's[6] and in Mage's[7] groups it was approximately 2 per cent. Increased operability and decreased mortality should mean an increase in the number of five-year survivors. However, this may not be the case because of the law of diminishing return. Allen[8] found that as the operability increased 10 per cent and the mortality decreased 10 per cent the number of five-year survivors increased only 1 per cent.

TABLE 1
AGE INCIDENCE

	21–30	31–40	41–50	51–60	61–70 and over
Original group.....	0.6%	4.6%	18.5%	34%	42.3%
Five-year survivors..	0	6.6%	40%	16.6%	36.6%

In addition to the twenty-eight five-year survivors, two who lived four years and nine months have been incorporated into the study, making a total of thirty.

Sex and Age. In a previously reported analysis of 466 cases of gastric carcinoma, the initial group from which the present survivors were obtained, 70 per cent were males. Of the thirty survivors 60 per cent were males, indicating that the survival rate in males is the same or slightly less than in females. The incidence of death from cancer of all types among males has increased more rapidly than in females according to a survey by Collins[9] and his collaborators.

Table 1 contrasts the age distribution in the survivor group with that of the original group in which the incidence of gastric cancer clearly rose from decade to

* From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago, Chicago, Ill.

decade. The irregular distribution in survival incidence with peaks in the fifth and seventh decades and a slump in the sixth is difficult to explain except on the basis of chance due to the small number of cases. Walters, Gray and Priestly[2] noted a higher proportion of five-year survivors in the sixth and seventh decades, the lowest survival rate being in patients below forty-years of age.

TABLE II
DURATION OF SYMPTOMS

	1–3 mo.	3–6 mo.	6–12 mo.	12–24 mo.	Over 24 mo.
Original series. . . .	24.5%	18%	26.2%	11.9%	19.1%
Five-year survivors	23.3%	3.3%	23.3%	20%	30%

SYMPTOMS

Duration of Symptoms. As shown in Table II 68.7 per cent of the original group had symptoms of less than one year's duration as compared with 50 per cent in the five-year survivors. In the former 42½ per cent had symptoms of less than six months' duration in contrast to 26.6 per cent of the latter. The group with symptoms of twenty-four months' duration or longer had a relatively better prognosis than those with symptoms of less than six months at the time of resection. Saypol and Hinton[10] found the resectability rate to be higher in those patients with symptoms of over six months than in those under six months. Walters et al. noted the five-year survival rate to be 24.6 per cent in those patients with symptoms of less than a year's duration and 32.1 per cent in those with symptoms of more than a year's duration. Faged and Larsen[11] in reporting upon 375 patients noted that 64 per cent had had symptoms of less than six months' duration; nevertheless, 50 per cent of these were inoperable at the time of first examination. These observations raise the question of the validity of the great emphasis placed on "early diagnosis." Symptoms depend upon many factors, such as location, obstruction, ulceration and anemia. It is a well recognized fact, of course, that gastric cancer may be far advanced before symptoms appear. Informative propaganda may bring the patient to the physician somewhat earlier; a good economic status may make for earlier diagnosis; however, these factors seem of minor importance compared with that of the fundamental biologic characteristics of the tumor.

Type of Symptoms. In the present group of thirty patients upper abdominal digestive distress was the chief complaint, being present in 93.3 per cent of the cases. In many, the distress was insidious in onset, unrelated or indefinitely related to food consumption and often inconstant in character. In some, the history suggested peptic ulcer, with periods of improvement noted after institution of ulcer therapy. Twenty-four described weight losses averaging from 10 to 20 pounds in a period of two to twelve months. Anorexia was marked in twelve patients. Three had no gastrointestinal complaints, presenting themselves with weakness and fatigue. Two noted tarry stools. These are the usual symptoms of gastric cancer and indicate that there are no special distinguishing symptoms in five-year survivors as compared with those who fail to survive. Saypol and Hinton[10] report the incidence of pain and digestive distress as 76.2 per cent and weight loss as 71.8 per cent.

PHYSICAL EXAMINATION

Palpable epigastric tumor masses were noted in 26.6 per cent of the five-year survivors as compared with 40 per cent in the original group. It is evident that large neoplasms are not a contraindication to surgical resection and, indeed, offer a fair prognosis. Lemon-tinged skin was marked in three patients. The liver was palpable but smooth in two. No lymph node involvement was detected in any of the group. Epigastric tenderness on palpation, a rather equivocal and unimportant finding, was present in eleven (36 per cent).

Anemia, Blood Loss and Gastric Acidity. Table III indicates that in thirty, five-year survivors at the time of initial examination four or 13.4 per cent had erythrocyte values below three million, thirteen or 43 per cent below 4 million, twelve or 40 per cent between 4 and 5 million and one or 3 per cent over 5 million. Nine or 30 per cent exhibited hyperchromic, seven or 23.3 per cent hypochromic and fourteen or 46.6 per cent normochromic blood pictures. Of the four patients with levels below three million no gastric free acidity on histamine stimulation was found in four; the stools, after meat-free diet, contained large amounts of occult blood as shown by the benzidine test. Polypoid ulcerated type I* carcinoma was present in two and type II in two others. In thirteen patients with values between three and four millions four were type I, eight others were type II while one was type III. The stools of nine were strongly positive with benzidine, three disclosed a trace and one had no blood. Of the last four patients three had type II and one type I carcinoma. Acid gastric juice was found with equal frequency in both types. In the twelve patients with red cell levels above four million there were six type II, three type I and three type III carcinomas.

TABLE III
ABSENCE OF RELATIONSHIP OF ERYTHROCYTE LEVELS TO THE TYPE OF TUMOR

Erythrocyte Level	Type I	Type II	Type III	Total
2–3 million	2	2	..	4
3–4 million	4	8	1	13
4–5 million	3	6	3	12
Over 5 million	..	1	..	1
Total	9	17	4	30

The stools of twenty-five patients were examined for occult blood by the benzidine test. In all instances the patients were placed on a meat-free diet for three days before the stools were collected and three or more specimens were examined. Large amounts of occult blood were found in fourteen, a trace only in eight and none in three. The degree of anemia, the presence or absence of occult blood and the level of gastric secretion was of little or no prognostic value as was shown by the five-year survival. The patients with polypoid lesions, however, did tend to be the most anemic.

Roentgenologic and Gastroscopic Manifestations. All of the thirty tumors were considered resectable by the roentgenologist. The operative findings confirmed the fluoroscopic and film diagnosis as to the site of the lesion: fourteen were antral, fourteen mid-gastric and two cardiac. Of the antral lesions two were type I Borrmann, nine type II and three type III. In the mid-stomach six were type I, seven type II and one type III. Of the two cardiac lesions one was type I and the second type II. The number of "curable" cancers found in the antrum was approximately the same as those found in the mid-stomach.

It is worth noting that in 20 per cent the initial x-ray findings were inconclusive in this group as compared with 8 per cent in the original group, thus suggesting earlier diagnosis and smaller lesions although subsequent measurements of the tumor apparently do not substantiate this point. Likewise in the survival group the initial gastroscopic examination was unsatisfactory in 40 per cent as compared with 15 per cent in the original group.

Gastroscopy disclosed the presence of atrophic gastritis in seven patients, in five it was absent and in six it was not recorded. Meissner[12] found the incidence of gastritis in patients with gastric cancer to be similar to that of patients with ulcer. The body and the fundus, however, were more often involved by the process.

DIFFERENTIATION FROM BENIGN ULCER

Allen in following a series of gastric ulcers over a ten-year period found that 14 per cent eventually proved to be carcinoma. Holman and Sandusky,[13] in a

* Gross classification of Borrmann, types I to IV inclusive.

study of 53 patients with gastric ulcer and 104 with carcinoma of the stomach, noted that the differentiation of ulcerating carcinoma and benign ulcer was not possible in 33 cases. Even at operation, in 23 of the 157 patients, the surgeon could not determine the true nature of the lesion. The problem of differentiation of the two lesions is not pertinent to this paper except to remark that in our series, as in all series, carcinomas were observed masquerading as benign ulcers. Some of the factors operative in such cases have been discussed elsewhere.[14]

TYPE OF TUMOR

The importance of the rate of growth, dependent upon unknown factors but obviously varying from cancer to cancer, is illustrated by the following cases:

One patient[15] was followed four and one-half years before assenting to laparotomy. During this period many x-ray and gastroscopic examinations disclosed an unusal lesser curvature ulcer which at times appeared benign and on other occasions looked like an ulcerating carcinoma. Histologically, the lesion was a well circumscribed colloid carcinoma. This case is an example of a slowly growing, almost benign carcinoma.

A second patient with a polypoid tumor of the antrum was observed for three years prior to operation. Repeated roentgenographic and gastroscopic examinations failed to reveal any significant change in the appearance of the lesion. Microscopic study revealed an adenomatous polyp with malignant changes. Apparently the rate of growth of the neoplastic tissue was an extremely slow one.

In contrast, one may cite the following case not included in this series in which a suspicious lesser curvature defect was demonstrated in a fifty-two year old male with symptoms suggestive of ulcer; exploration was advised but refused; a second examination two months later disclosed some decrease in the size of the lesion. Three months later, five months after the initial examination, both x-ray and gastroscopy demonstrated a large tumor mass in the mid-stomach and operation revealed an inoperable type IV carcinoma with liver metastases.

In 20 per cent of five-year resection survivors indefinite findings or other factors resulted in a delay of three months to four and one-half years before operation, yet all survived five years or more after resection. This further emphasizes the importance of the innate character of the tumor.

When the thirty five-year survivors are grouped according to the gross classification of Bormann (seen in the illustration on page 234), twenty-six fall into types I and II, a finding in accord with others and in contrast to the total incidence of the various types as described by Schindler: 2.99 per cent type I, 17.6 per cent type II, 16.3 per cent type III and 63.2 per cent type IV. This apparently suggests that the gross, or Borrmann, classification may be of considerable prognostic value. In a comparison of the five-year survivors with a group who survived for less than one year after resection, however, the correlation was not as striking. Histologic studies of the two groups were then made and are being reported in detail elsewhere.[15]

In general the tumors resected from patients who survived five years or more tended to be sharply circumscribed. In an occasional case the tumor cells showed marked degenerative changes resembling those of prostatic carcinoma after orchiectomy. Histologically, the tumors from the five-year survivors were of all types, including adenocarcinoma, fourteen; undifferentiated carcinoma, six; round cell carcinoma, three; colloid carcinoma, three; mixed cell carcinoma, three and infiltrating carcinoma, one. In contrast, the group who survived less than one year contained eleven infiltrative lesions. This illustrates again the tremendous importance of the inherent nature of the tumor itself.

A comparison of the sizes of the lesions in the different groups showed surprisingly little variation. Nine type I tumors varied from 10 by 9 by 6 cm. to 1.5 by 1.5 by 2

cm., with a mean of 5 by 5 by 7 cm. Seventeen type II tumors ranged from 9 by 6.5 in diameter to 1.5 by 2 cm., averaging 7 by 5 cm. Four type III lesions averaged 4 cm. in diameter. MacCarty[17] found the mean diameter of a large group of resected tumor metastases to the transverse colon by a type II lesion survived partial gastrectomy and partial colectomy and was well ten years later.

In two patients at operation the stomach was found attached to the liver, necessitat-

Gross Classification of Gastric Carcinoma - BORRMANN	Incidence in all gastric Ca.	Incidence in 30 5 year survivors
TYPE I 	2.9%	30.% (9 cases)
II 	17.6%	56.8% (17 cases)
III 	16.3%	6.66% (4 cases)
IV 	63.2%	0

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lesions to be 6 cm. with a slight decrease in the size of those encountered in the later years of his study. Our study suggests that the size of the lesion is of little importance in determining the degree of malignancy or life expectancy. Apparently even the "curable" cancer approaches 6 cm. in diameter before detection.

Seven or 23 per cent of the survivors had evidence of lymph node metastases, mesenteric involvement or spread to the neighboring organs at the time of operation. Of six with lymph node involvement five were type II and one was type I Borrmann. Survival after resection was more than five years in one, seven years in three and eleven years in a fifth. A sixth (type I) with mesenteric involvement at the time of partial gastric resection developed recurrence in the gastric stump with involvement of the liver twelve years later.[18] The seventh with

ing resection of a portion of that organ, averaging 5 by 5 by 3 cm. in each case. Histologic examination showed only inflammatory reaction and no evidence of liver metastases. Here the importance of removing carcinoma with resection of the liver, when feasible, is demonstrated. The desirability of palliative resection when portions of neoplastic tissue are knowingly left behind is considerable. Anschütz[19] reported that 21 per cent of ninety-nine such patients survived three years and 8 per cent survived five years, in contrast to death within one year as occurred in untreated patients.

POSTOPERATIVE STATUS

Two of the thirty patients (6.6 per cent) developed marked anemia. The first, with a type II tumor of the antrum necessitating removal of the distal half of the stomach,

had on admission a free acid value of 50 clinical units and an erythrocyte count of 3.8 million with 12 Gm. of hemoglobin. The anemia, which developed postoperatively, (3 million red cells and 10 Gm. hemoglobin), was at first considered due to an inadequate diet; however, there was no response to parenteral liver, iron or diet. Four years later the erythrocyte and hemoglobin values were unchanged. The second, a fifty-six year old male had on admission red cell count of 3.9 million with 13 Gm. of hemoglobin. A 5 by 3 cm. type II carcinoma of the posterior antral wall was found at laparotomy and the distal two-thirds of the stomach was resected. After operation the erythrocyte level declined to less than 3 million. The patient responded favorably to parenteral liver extract and has maintained an erythrocyte level of over 4.5 million with this therapy.

Two patients were known to have pernicious anemia before resection. One had been followed in the Hematology Clinic for three years when he noted a mass in the left upper abdomen. Laparotomy proved this to be a type I carcinoma 10 cm. in diameter; the lower two-thirds of the stomach was resected. The patient has been adequately maintained on liver extract for four years and nine months after operation with no apparent ill effect from gastrectomy. A second patient previously described[18] was found to have pernicious anemia and a polypoid gastric lesion. At operation six months later this was removed and found to be a polypoid adenocarcinoma with myxomatous degeneration. Eight years later a type I carcinoma necessitated partial resection of the stomach. Nine years after the resection gastroscopy disclosed several polyps in the remaining stomach; three years later, twenty years after the first operation and twelve years after the second, recurrence of the lesion with metastases necessitated a third operation which the patient did not survive.

One patient with total gastrectomy was among the five-year survivors. On admission his red count was 3.84 million and hemoglobin 7.4 Gm. No free acid was present on histamine stimulation. A large type I cardiac lesion required removal of the entire stomach with splenectomy. Local lymph node metastases were present. The patient has remained in good health with no evidence of anemia or digestive disturbances in the five years following operation. Joll and Adler,[20] in reporting two cases surviving three years and two months and three years and six months, respectively, following total gastrectomy, found records of forty-seven others described between 1933 and 1942.

In a study of the economic status of the group it was found that eighteen had no symptoms and were self-sustaining economically. Six others complained of moderate to severe digestive disturbances which limited their working capacity but allowed economic independence. Two had persistant fatigue and failed to gain weight but were able to support themselves partially. Two others developed myocardial infarcts. One had coronary insufficiency for many years and survived a gastric resection for seven years. He remained a chronic invalid during the entire postoperative period and died following cardiac infarction. The second survived infarction three years after gastrectomy and has been able to carry out a fair portion of his duties.

Two patients developed recurrent carcinoma six and nine years, respectively, after resection. The former, a forty-one year old housewife, was subjected to subtotal gastrectomy eighteen months after the onset of digestive symptoms. A second operation six years later revealed metastases to the ovaries, a Krukenberg's tumor. The stomach was not involved. The latter patient[18] has been previously described. Here the lesion was confined to the stomach.

Eighty per cent (twenty-four) of the survivors were restored to useful life for five years or more after operation.

SUMMARY

Of 377 patients with gastric carcinoma 115 or 30.8 per cent survived resection;

twenty-eight, 7.4 per cent of the 377, survived five years.

Fifty per cent of the five year survivors had had symptoms of over a year's duration as compared with 31 per cent of the initial group. The symptoms were essentially identical in type. Palpable tumor masses were present in 40 per cent of the original group as compared with 26.6 per cent of the survivor group.

Nine of the survivors had type I (Borrmann) carcinoma, seventeen had type II and four had type III; there were no five-year survivors in the Borrmann type IV group.

Metastases were present in 23 per cent of the five-year survivors, five with lymph node involvement, one with mesenteric involvement and a seventh with spread to the transverse colon.

Eighty per cent of the five-year survivors were restored to useful life.

CONCLUSIONS

1. Contrary to what might be expected in gastric cancer, patients with symptoms of long duration tend to show a higher percentage of five-year survival than do those with symptoms of short duration.

2. Presence of a palpable tumor mass is not a contraindication to operation or resection.

3. The initial erythrocyte values, hemoglobin levels and gastric free acidity have no prognostic import.

4. The type of carcinoma is of the greatest prognostic significance, the long survivors consisting chiefly of those with type I and type II tumors (Borrmann).

5. The size of the lesion varies widely even in "curable" cases.

6. The need for further study of the factors responsible for the variable rate of growth in different tumors is evident. The rate of growth is the most important factor in determining the duration of survival. This fundamental problem is, of course, inseparably linked with that of the cause of cancer.

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Benign Pelvic Tumors with Ascites and Hydrothorax*

Meigs' Syndrome

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THE syndrome of fibroma of the ovary associated with ascites and hydrothorax is one which has only recently been brought to the attention of the internist, gynecologist and surgeon through the work of Meigs and associates.[2–7] The importance of a thorough knowledge of this condition is at once apparent since a tumor giving rise to distant effusions has heretofore been associated with grave prognostic implications and has usually carried a stigma of inoperability.

The first account of this syndrome was published by Cullingsworth[1] in 1879. His patient complained of masses in the lower abdomen and of uterine hemorrhage. Later her abdomen began to swell, she lost weight, developed a left pleural effusion, became intensely dyspneic and, after three months, died. Operation was considered to be unwarranted. How many more such cases occurred and are occurring without their true significance being recognized may only be speculated upon. It is encouraging, however, that recognition of this syndrome is now growing because, following Cullingsworth's report, only five more cases were described before 1932 and since that time some fifty to sixty cases have been added to the literature. This has been due chiefly to the orderly work of Meigs and his group which was first published in 1937 although previous observers in recent times such as Leo in 1926[10] and Salmon[12] knew of this syndrome. On the basis of these reported cases it has been shown that this syndrome usually occurs in women past the menopause. The symptoms have chiefly been dyspnea and swelling of the abdomen although weakness, chest and abdominal pain and cough have been present; the duration of symptoms ran from a few days to several years in one of Meigs' cases.[5] The location of the tumor has been about equally divided between the two sides and in about 10 per cent of cases has been bilateral. The pleural effusion has usually been on the right side. In 10 per cent of the cases it has occurred only on the left while in 15 per cent the effusion has been bilateral.

In 1943 Rhoads and Terrill[13] presented a case and first termed the condition "Meigs' Syndrome." This name has endured and justly gives credit where due; however, it has resulted in some confusion in nomenclature. Meigs' group has continued to include in the syndrome only a fibroma of the ovary. Others have broadened the term to include any benign pelvic tumor giving rise to ascites and to hydrothorax. We agree with the latter viewpoint since, so far as is known, the mechanism of the effusions remains the same regardless of the type of the tumor. Meigs' syndrome has, therefore, been reported to include thecomas[23–25] myomas of the uterus,[24,26] Brenner tumor[22] and struma ovarii[24] as well as the ovarian fibromas as originally described. That the same syndrome may arise with pelvic malignancies without metastasis to the chest should be kept in mind.[7]

CASE REPORTS

CASE 1. K. B., a fifty-two year old, single, practical nurse, entered the Barnes Hospital, June 9, 1943, with the complaint of dyspnea on exertion of two week's duration. During the same period she also complained of fatigue and a dull, aching pain in the lower left chest posteriorly. The chest pain and dyspnea appeared quite suddenly while she was walking and had never been present before.

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The family history was relevant in that a sister had pulmonary tuberculosis in 1934. The patient had intimate contact with this sister in the early stages of her disease.

The past history is of interest in that an operation was performed in 1939 at which time the uterus, right tube and right ovary were removed. The surgeon noted no abnormality of the left ovary at that time. There were never any symptoms suggestive of pulmonary tuberculosis. Normal menopause occurred at the age of forty-seven years. There had been a steady weight gain from 140 pounds at the age of thirty years to the present weight of 210 pounds.

Physical examination revealed a temperature of 36.5°C. (97.6°F.), pulse of 88 per minute and respirations of 20 per minute. The blood pressure was 150/92. The patient was generally obese. There was slight widening of the arteriolar reflexes of the retinal vessels. The tonsils showed moderate hypertrophy but were not inflamed. The chest was symmetrical with equal expansion of the two sides. There was marked dullness to percussion up to the fifth rib posteriorly on the right and impaired resonance up to the apex at which point a few moist râles were heard. On this side the percussion note was dull in the axilla and also up to the second rib anteriorly. Fremitus and breath sounds were decreased in intensity over this area but the character of the breath sounds was not changed. The left chest was entirely clear. The abdomen was soft and protuberant. There was no rigidity but there was tenderness over the right upper quadrant and over the left lower quadrant. Just above and to the left of the symphysis pubis was felt a slightly irregular, movable, firm, orange-sized mass. No signs of free fluid in the abdomen could be detected. Pelvic examination revealed a firm, non-tender mass in the left adnexal region which seemed to be continuous with the abdominal mass. A normal cervix with a polypoid structure protruding from the external os was visualized. Rectovaginal examination revealed a firm, freely movable mass, 6 to 8 cm. in diameter, high in the left adnexal region. There were numerous varicosities over both lower extremities.

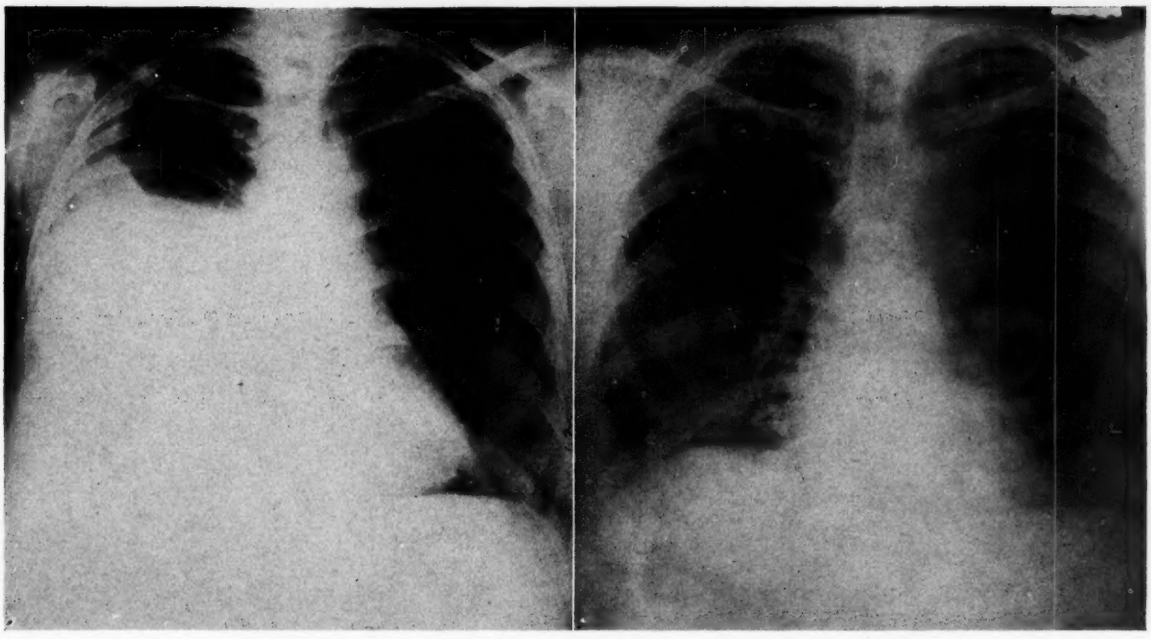
Laboratory data revealed a complete blood count, urinalysis and stool examination to be normal. The Kahn test was negative, nonprotein nitrogen was 18 mg. per cent and the fasting blood sugar 95 mg. per cent. The first strength PPD (tuberculin) test was negative after forty-eight hours. The sedimentation index was 1.5 mm. per minute (Wintrobe). Total plasma proteins were 5.6 Gm. per cent, with albumin 3.5 Gm. per cent and globulin 2.1 Gm. per cent. Vital capacity was 1,925 cc. (probably submaximal due to chest pain). The venous pressure was 70 mm. of saline, the ether circulation time was 7 seconds and the decholin time 10 seconds.

Fluid was aspirated from the right chest on the third, fifth and tenth hospital days. The volumes of fluid withdrawn were 550 cc., 1,975 cc. and 500 cc., respectively. On the first two thoracenteses, the fluid was yellow, slightly turbid, with a specific gravity of 1.013 and a cell count (after hemolysis with 0.1 N HCl acid) of 60 lymphocytes per cu. mm. Microscopic section of these sediments revealed no malignant cells. Aerobic and anaerobic cultures of all three samples of fluid yielded no growth.

The third fluid was serosanguineous with a specific gravity of 1.018 and a cell count (after hemolysis with 0.1 N HCl acid) of 2,200 per cu. mm. Differential count of these cells revealed 65 per cent eosinophiles and 17 per cent lymphocytes; the remainder were degenerated leukocytes. A guinea pig injected with fluid from the first thoracentesis was negative for tuberculosis. Chest films, taken before the first and after the second thoracentesis, failed to reveal any lung lesions. (Fig. 1.)

With the above information at hand, a preoperative diagnosis of Meigs' syndrome was made and the patient was transferred to the gynecologic service. At operation about 200 cc. to 300 cc. of clear, free abdominal fluid were encountered and the left ovary was found to be solid, smooth and the size of a small grapefruit. There was no evidence of metastases. A left salpingo-oophorectomy and conization of the cervix were performed by Dr. Carl Wegner. There was no ovarian tissue, as such, found in the mass, and grossly and microscopically it was a typical fibroma. Microscopic study revealed the tube to be normal.

The postoperative course was entirely uneventful. There was no clinical or fluoroscopic evidence of reaccumulation either of the pleural or abdominal effusions. A roentgenogram of the chest, taken fifteen weeks after operation (Fig. 1), showed no residual abnormalities. The patient resumed her duties as a practical nurse six weeks after the operation and has remained perfectly well ever since.



A B

FIG. 1. X-rays of the chest of Case I. A, before the first thoracentesis; B, fifteen weeks postoperatively.

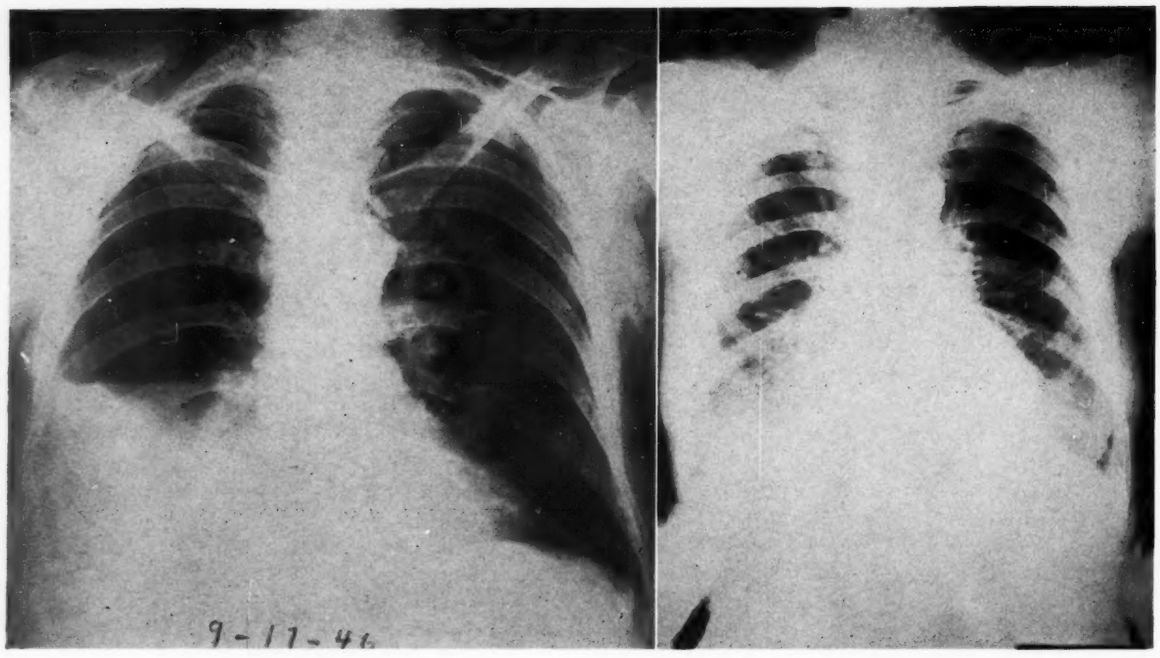
CASE II. E. L., a sixty-four year old widow, was seen in the Washington University Clinics on September 10, 1946, and was admitted to the Barnes Hospital the following day with complaints of enlargement of her abdomen of nine months' duration and of dyspnea on exertion for four or five months' duration. She had no other symptoms except loss of appetite, a weight loss of 15 pounds during the past six months and a slight non-productive cough of a few months duration. The enlargement of the abdomen had been painless. Just prior to the appearance of dyspnea she saw her family doctor who told her that she had a tumor of the uterus and advised surgery.

The family history was of interest in that her husband had died twenty-five years previously and was said to have had tuberculosis.

The menstrual history revealed a menarche at fifteen years of age with a normal and regular cycle. The menstrual periods ceased eleven years ago without incident except that two years later she had one apparently normal period. She had five pregnancies with normal deliveries.

Physical examination revealed a temperature of 37.6°C. (99.6°F.), pulse of 86 per minute and respirations of 24 per minute. The blood pressure was 124/76. She was poorly nourished, slightly dyspneic and had a distended abdomen. The fundi showed some arteriosclerotic changes. The heart revealed a moderately loud systolic murmur heard best at the apex. The entire right chest was flat to percussion anteriorly and posteriorly and showed absent tactile fremitus. The breath sounds were absent over the lower half of the right chest and over the upper half they were depressed, high pitched and tubular in character. The left lung field showed no abnormalities. The abdomen was markedly distended and showed bulging of the flanks. There was shifting dullness to percussion and a fluid wave. A large, irregular, firm mass was felt in the lower abdomen which extended a little to the right of the midline and above the umbilicus. Pelvic examination showed a moderate rectocele and the cervix pointing downward and to the right. The mass could be felt with the vaginal finger but it was too large to enable the examiner to make out any details.

Laboratory data included a complete blood count, urinalysis and stool examination which were normal. The Kahn test was negative. Thoracenteses were done on the first (1,300 cc.), second (1,500 cc.), third (2,000 cc.), seventh (1,800 cc.) and thirteenth (1,650 cc.) hospital days. All of these fluids appeared identical in that they showed a small amount of gross blood, specific gravity of 1.014 to 1.018, an average count of 300 cells per cu. mm. (after hemolysis with $\frac{1}{10}$ N HCl acid), with a differential count of 52 per cent mononuclear cells and 48 per cent polymorphonuclear cells on the



A B

FIG. 2. X-rays of the chest of Case II. A, before the first thoracentesis; B, fourteen weeks postoperatively.

first fluid. The non-protein nitrogen of the fluid was 19 mg. per cent. Microscopic sections of the cellular sediment showed no malignant cells. The blood non-protein nitrogen was 19 mg. per cent and the total protein was 5.4 Gm. per cent with 3.3 Gm. per cent of albumin and 2.1 Gm. per cent of globulin. Fluoroscopy and x-ray of the chest, after the fluid level in the right pleural cavity had been lowered by the introduction of air, showed no abnormalities in the lung fields. (Fig. 2.)

On the eighth hospital day the patient was transferred to the gynecologic service with the diagnosis of Meigs' syndrome. Uterine and ovarian malignancies were considered as possibilities.

On the fourteenth hospital day the patient was operated upon by Dr. William Masters. Caudal anesthesia was used. The entire peritoneal cavity was found to be filled with straw colored fluid. When this was removed, a large, tense, right ovarian cyst was found which measured about 10 by 12 cm. (Fig. 3.) This tumor and the right tube were easily removed. Examination of the remainder of the abdominal cavity revealed no evidences of metastasis or other abnormality.

Recovery of the patient was uneventful. On the sixteenth hospital day (second postoperative day) a right thoracentesis was done but only 10 cc. of straw colored fluid were obtained.

The patient was discharged from the hospital on her twenty-seventh hospital day with diagnoses of (1) Meigs' syndrome; (2) pseudomucinous cystadenoma of the right ovary and (3) right, chronic salpingitis. Six weeks after operation she was again seen at the Washington University Clinics at which time she had gained 10 pounds, felt well, lost her cough but still had a right pleural effusion. Twelve weeks postoperatively she was again examined and the pleural effusion was found to be still present. Therefore, it was planned that she was to be hospitalized again for further study but, at fourteen weeks postoperatively, the fluid had been absorbed, the chest was clear, she felt well and appeared to have completely recovered. (Fig. 2.)

COMMENTS

The first case showed two interesting features: In the first place the abdominal exploration done in 1939 by a capable surgeon failed to reveal any abnormality of the left ovary and yet in four years this benign growth had reached a size of 9 by 10 by 12 cm. and had been associated with effusions into the chest and abdomen. Secondly, the last thoracentesis performed before operation revealed an eosinophilic transudate into the pleural cavity. The

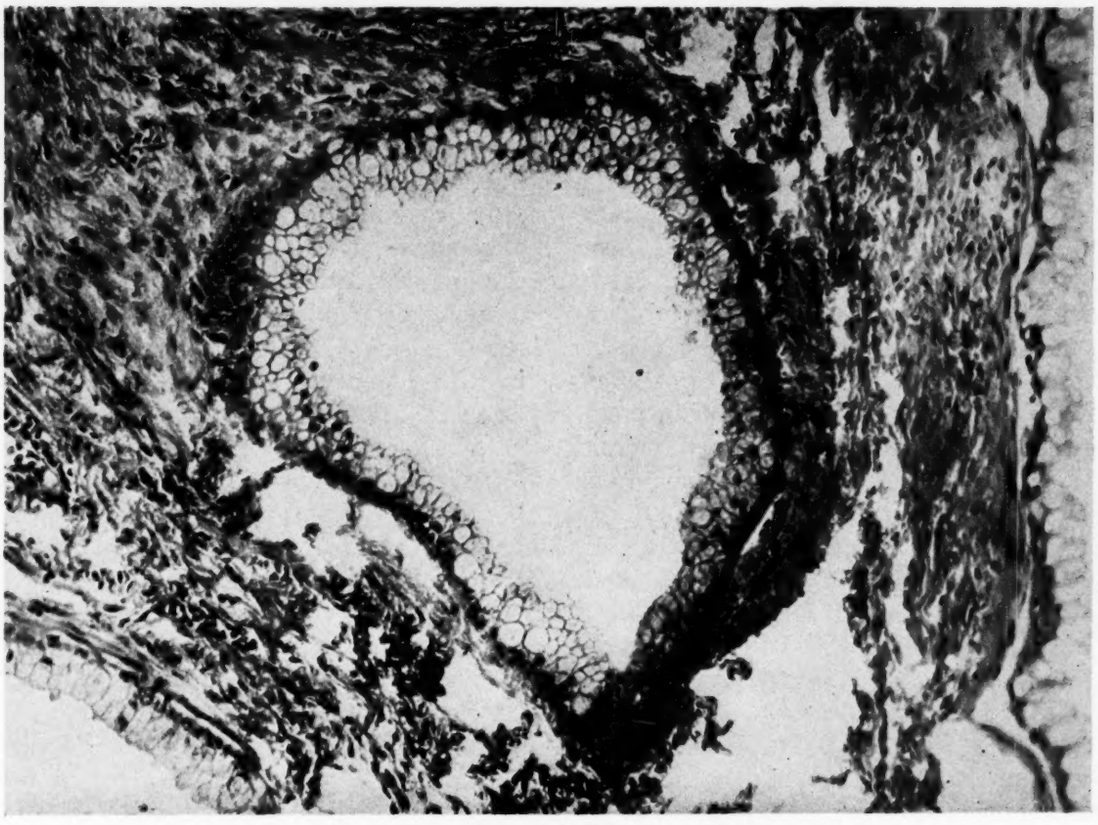


FIG. 3. Photomicrograph of tumor in Case II.

second patient adds another case to those already reported to emphasize that any benign pelvic tumor may give rise to this syndrome.

By far the most interesting problem relating to this syndrome is the pathogenesis of the pleural effusion. Meigs was originally of the opinion that not all fibromas of the ovary are accompanied by ascites and, even fewer, by pleural effusion. In a later paper, however,[5] he quotes Dr. Thomas S. Cullen who said, "Nearly every case of fibroma of the ovary that I have seen has been accompanied by abdominal fluid," but modifies this statement with his own experience and concludes that about 75 per cent of fibromas of the ovary are accompanied by ascites but, of these, only a few show hydrothorax and that this occurrence is dependent upon circumstances which will be discussed later. At any rate, the occurrence of effusions with this tumor is far too frequent to be coincidental.

In some cases ascites alone is found and the explanations given are manifold, i.e., inflammation, twists of the pedicle and adhesions to surrounding structures. Rubin, Novak and Squire[24] cite an important observation made by Geibel[32] which is also quoted in Miller's handbook.[31] Geibel placed two ovarian tumors in dry containers and in twenty-four hours one tumor secreted one-third of its weight in clear amber fluid. Geibel explained this as being due to extreme cystic dilatation of lymph spaces with ensuing nutritional disorders or necrosis of edematous tissue. In keeping with this observation we think it significant that a great many of the reported cases revealed either frank cysts in an otherwise firm tumor or, at least, microscopic dilatation of the lymph spaces. It is of interest that the photomicrographs of our second case, (Fig. 3) show markedly edematous tissues surrounding the cyst in the section. With regard to fibromas and theca cell tumors, Rubin[24] makes the statement, "Considering the fact that the tumor is fibromatous, it is

conceivable that constriction of the afferent lymph or blood vessels takes place in the tumor itself or in its pedicles, and then produces congestion and lymph stasis which may be followed by exudation of tissue fluid on its surface." The reason for the pleural effusion, on the other hand, is more obscure. Many explanations have been suggested; some of them may be easily discarded and others are interesting but so far lack satisfactory proof. They are as follows:

Obstruction of the Azygos Vein. This vein, into which flows the hemiazygos vein from the left side, carries all the blood from the parietal layers of the pleurae and, therefore, might conceivably give rise to pleural effusions if partially or completely blocked. In fact, one patient[5] was found to have such an obstruction but it is difficult to see how such an obstruction could frequently result from a benign pelvic tumor.

The Alarm Reaction of Selye. Selye[27] observed that animals exposed to physical or chemical trauma developed a shock-like state associated with the accumulation of pleural and peritoneal effusions. With continued exposure to the agent, the animals gradually became readjusted and bodily functions approached normal. After three months these animals lost their resistance and succumbed with shock-like symptoms plus accumulation of peritoneal and pleural transudates. Selye, as well as Meigs,[5] have proposed that the ovarian fibroma itself may act as a noxious agent or perhaps may secrete one which gives rise to the effusions in the chest and abdominal cavities in a manner similar to that observed experimentally by Selye.

Perforations in the Diaphragm. This possibility must be considered since minute perforations between the peritoneal and the pleural cavities have been demonstrated by careful anatomic dissection. Rubin[24] states that these minute canals have been demonstrated in both leaves of the diaphragm but are much more numerous on the right; the network of lymph spaces are present throughout the diaphragm except in the tendinous center portion. Meigs, Armstrong and Hamilton[5] found a large opening in the diaphragm of one of their patients which communicated with the mediastinum. In this, and others of their cases, India ink was injected into the peritoneal cavity and soon after was found in approximately the same concentration in the mononuclear cells of the pleural fluid. Frequent blood studies following the injection, however, failed to reveal a single instance of carbon particles in the leukocytes of the blood stream. Likewise, the work of Lemon[28] has indicated that, in animals at least, some sort of one-way communication may exist between the peritoneal and pleural cavities because he has demonstrated the passing of particulate matter in that direction but was unable to find that such particles passed in the opposite direction. In some cases[5] air was introduced into one of the body cavities after which the patient was tilted into various positions, but no air could ever be demonstrated to have passed to the other cavity. Likewise, Rubin[24] injected kaolin into the abdominal cavity of animals in which he had been able to demonstrate the passage of small India ink and carmine particles from the abdomen to the chest. Following injection of the kaolin, he could no longer show the passage of smaller particles nor the passage of kaolin particles into the chest cavity. These experiments led him to conclude that the pleuroperitoneal canals were very small and would not permit the passage of air and could be blocked by larger particles such as kaolin.

How else then is the pleural transudate to be explained? Fluids from the abdomen and chest of the same patient have repeatedly been shown to be identical as regards their protein content and specific gravity. The typical fluid has been a simple, amber-colored transudate although serosanguineous effusions have been described in about 15 per cent of cases including our second case. Also electrophoretic studies on the fluids have shown identical protein fractions.[5,24] In only two cases[12,24] was the pleural fluid different from that found in

the abdomen. The preponderance of the evidence would seem to indicate that the fluid passes from the abdomen into the chest. If this is true, some additional explanations must be made. How is it that patients have complained severely of dyspnea and some have had numerous thoracenteses without any apparent increase in the size of the abdomen or even a sensation of abdominal fullness? How is it, as in our own first patient, that three thoracenteses could be performed in a period of less than a week but yet at operation only 200 cc. to 300 cc. of fluid could be found in the abdomen? Again, how is it that patients with hepatic cirrhosis and with abdomens enormously distended by ascites rarely develop pleural effusion unless on the basis of hypoproteinemia or some other more obvious cause? These are problems which must yet be answered before one assumes that the ascites becomes pleural effusion by the simple expedient of passing through the diaphragm. It is our belief that this may make the problem well worth investigating further. Whatever the method of formation of the pleural fluid may be, it is often rapid since certain of the cases have shown a complete refilling of the chest in twenty-four hours and repeated thoracenteses have been carried to the point of causing dehydration and protein imbalance.

Such obvious explanations as hypoproteinemia, cardiac and renal disease have repeatedly been excluded and no longer are to be considered as causes for the effusions.

We have not been able to explain the suddenly developing eosinophilic pleural effusion in our first case. Unfortunately, there was no differential count of the blood made just prior to the withdrawal of the eosinophilic fluid but previous and subsequent counts failed to show any unusual blood eosinophilia. It has been suggested that this 65 per cent eosinophilia of the pleural fluid developed as an allergic response to the introduction of novocain during thoracenteses. Also, we considered that this might indicate an infection, particularly a tuberculous infection but such did not seem to be the case. In Loeffler's syndrome, which frequently gives rise to eosinophilic pleural effusions, there is an accompanying allergic pneumonitis but this was not present in our own case. It is of interest that in the case of Gild[21] the first thoracentesis produced an opalescent fluid with 82 per cent eosinophiles. Two explanations have been offered for the spontaneous eosinophilic effusions: (1) The theory of Ehrlich and Naegeli[29–30] which holds that there is some chemotactic influence which locally attracts the normal eosinophiles formed in the bone marrow. (2) The theory of Widal and Faure-Beaulieu[29–30] which is generally adhered to and which holds that the eosinophiles have a local origin in response to some unknown stimulus, and may be formed from any of the leukocytes, hemohistioblasts or from connective tissue cells.

So far as we know there is none other than a coincidental relationship between our case of Meigs' syndrome and the appearance of eosinophiles in the pleural effusion.

SUMMARY

1. Two new cases of Meigs' syndrome are presented and theories as to the pathogenesis of the syndrome are discussed.

2. In one of the cases it is of particular interest that the patient had been operated upon four years previously at which time the left ovary was found to be normal. During the intervening four years the ovary grew to the size of a small grapefruit and was shown at operation to be replaced by a typical fibroma.

3. During the preoperative course of the first patient a right pleural effusion, noted on admission, changed character from that of a simple transudate to a serosanguineous effusion with 65 per cent eosinophiles. No explanation is offered for the change in the nature of the effusion.

4. The second patient had a pseudomucinous cystadenoma of the right ovary with massive ascites and right pleural effusion.

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Metabolic and Inflammatory Histiocytosis*

With Case Reports of Gaucher's Disease, Letterer-Siwe's Disease and Eosinophilic Granuloma†

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THE histiocyte or pyrrole cell or macrophage (Metchnikoff) is a tissue cell of the reticulo-endothelial system which is phagocytic to foreign particles of all sorts. With the lymphocyte it contributes to the repair process which follows the acute phase of a tissue injury. The epithelioid and giant cells of certain inflammatory processes are derived from the histiocytes.

Among the diseases of the histiocytic or reticulo-endothelial system, certain conditions have been grouped as metabolic disorders. These are the lipidoses[1] or lipoid histiocytosis, Gaucher's disease, Niemann-Pick's disease and Hand-Schüller-Christian's disease. However, in recent years, Jaffe and Lichtenstein,[2] Otani and Ehrlich[3] and others have described a benign granuloma of bone, now generally called eosinophilic granuloma, with pathological features closely related to Schüller-Christian's disease. It has also been shown that Letterer-Siwe's disease (variously termed aleukemic reticulosis, non-lipoid histiocytosis and reticulo-endotheliosis) bears a strong resemblance to both Schüller-Christian's disease and eosinophilic granuloma. These three conditions are non-familial and show no racial predilection. Histologically, Schüller-Christian's disease, Letterer-Siwe's disease and eosinophilic granuloma of bone are inflammatory granulomata. There is good reason to believe that they are of infectious origin. The profusion of designations for these conditions has introduced confusion concerning them. I have thought it proper and useful to discuss and relate these several disorders because these granulomas are not rare and present problems of differential diagnosis. They simulate true neoplasms. They may be confused with myeloma, Ewing's sarcoma, giant cell tumors of bone, metastatic involvement of the spine and tuberculosis. They are not true tumors as they increase in size by the addition of cells and not by cell division.

The essential lipoid histiocytoses, Gaucher's and Niemann-Pick's disease, are believed to be inherited metabolic disorders because of their familial occurrence and their predilection for those of the Jewish race. All of our patients with Gaucher's disease were Jewish, one of whom showed a familial incidence.

Schüller-Christian's disease has been considered a storage disease involving cholesterol, the analogue of Gaucher's disease which is a lipoid disturbance of the cerebrosid kerasin and Niemann-Pick's disease, the lipoid of which is a phosphatid-lecithin.

With the principal exception of Thannhauser,[1] this view is no longer held. As Mallory[4] has indicated, Schüller-Christian's disease and, by implication, Letterer-Siwe's disease and eosinophilic granuloma of bone are not "simple so-called storage diseases." The lesions exhibit characteristics of a granulomatous process accompanied by significant grades of inflammatory reaction, both leukocytic and fibrotic. Yet the induction of cholesterol storage by feeding

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cholesterol to rabbits does not result in a granulomatous, inflammatory reaction. It is significant that the spontaneous familial disease of man characterized by cutaneous xanthelasma, hypercholesterolemia and extensive deposits of cholesterol in tendon sheaths and other tissues, i.e., familial xanthomatosis, is not associated with granulomatous reactions and never shows the destructive lesions of bone that characterize Schüller-Christian's, Letterer-Siwe's and eosinophilic granuloma. No familial or racial tendencies have been noted in the latter group of diseases in contrast to the storage group. Biopsy of a fresh lesion shows a granulomatous reaction but little or no lipoid deposit. Cholesterolization occurs only with progression of the disease and is secondary and not primary.

It has been suggested,[2] and this paper will further demonstrate, that there is a close relationship between Schüller-Christian's disease, Letterer-Siwe's disease and eosinophilic granuloma. The pathologic processes are similar and the clinical manifestations show a considerable degree of overlapping. It would appear that the three entities represent clinical syndromes which are variations of the same basic disorder which might collectively be termed inflammatory histiocytosis.

Our first case illustrates the metabolic disorder, Gaucher's disease. The clinical features of this lipoid histiocytosis are hepatosplenomegaly with normal liver function, anemia, leukopenia, thrombocytopenia and a hemorrhagic tendency. There is a familial incidence, pingueculae, which are yellow, wedge-shaped areas at the margins of the cornea, brown pigmentation of the skin and bone lesions which are frequently localized to the lower part of the femur. These characteristics are well illustrated by our first patient.

CASE REPORTS

CASE 1. The patient, a thirty-four year old male, was first admitted to the hospital on August 2, 1944. He felt well until November, 1943, when he developed a severe hemorrhage from the gums following a tooth extraction which necessitated two blood transfusions. His white blood count dropped to 1,500. This was attributed to the administration of sulfathiazole. In 1937, he had complained of pain in the right hip for two weeks' duration. An x-ray was taken and he was told that he had Perthes' disease. Examination at the Hammond General Hospital in the army revealed pigmentation of the skin, a greatly enlarged spleen, leukopenia, between 2 to 5,000, with 40 per cent polymorphonuclears. Bleeding time was three minutes and clotting time was twenty-eight minutes. There were 49,000 platelets and there was no clot retraction in twenty-four hours. Bone marrow biopsy revealed characteristic Gaucher cells. Splenectomy was done on February 1, 1944. The spleen weighed 3,960 Gm. Chemical examination of the spleen showed that 50 per cent of this was made up of a glycolipid. Microscopic examination showed characteristic Gaucher's cells throughout the spleen. He was given several blood transfusions and the abnormal hematologic findings improved.

On admission to this hospital, he stated that a half sister had a son with Gaucher's disease. Upon standing he complained of a dull pain in the right hip which radiated down the right leg. Examination at this time revealed a diffuse, brownish pigmentation of the skin. There were no pingueculae. The liver was four fingerbreadths below the costal margin and was slightly tender. There was slight atrophy of the right thigh and leg. There was tenderness and a slight protuberance over the right hip. X-ray showed flattening of the head of the right femur. There were numerous cyst-like areas throughout the head. The lower halves of both femurs showed widening of the shaft, thickening of the cortex and the characteristic Erlenmeyer flask appearance. (Fig. 1.) The blood count was 7,800 white blood cells, with 50 per cent polymorphonuclears, 40 per cent lymphocytes, 6 per cent monocytes, 4 per cent eosinophiles. There were 270,000 platelets. Coagulation time was four minutes and bleeding time was one minute. He was furnished with a lift to the right shoe and was discharged. He was readmitted January 11, 1945 because of pain in the left hip of four weeks' duration. The alkaline phosphatase was 30.2, acid phosphatase 5.1 (King-Armstrong units), cholesterol 210, cholesterol esters 162. Cephalin flocculation was negative.

The patient improved with conservative therapy and was discharged February 17, 1945.

Another of our cases of Gaucher's disease, which will be reported elsewhere, is of considerable interest in that the patient developed an osteogenic sarcoma in an area of osteolytic involvement.

Letterer-Siwe's disease is an inflammatory histiocytosis which occurs only rarely beyond the age of two years and usually runs a rapidly fatal course. It is characterized by fever, rash, progressive weakness, enlargement of the spleen and superficial lymph nodes and secondary anemia. There are one or more destructive lesions of the bones. These occur most commonly in the skull with or without lipoid deposits. Mottling or honeycombing and emphysema are seen in the lungs. Every grade of transition between Letterer-Siwe's disease and Schüller-Christian's disease is observed, particularly after the age of three or four years when the disease becomes chronic and the picture of Schüller-Christian's disease is more and more frequent. It is emphasized, therefore, that Schüller-Christian's disease is a syndrome characterized by the involvement of the base of the skull and the hypophyseal region by the granulomatous process, producing the characteristic triad of exophthalmos, diabetes insipidus and cystic lesions of the skull. There is a hypercholesterolemia* with secondary lipidization of the histiocytes with cholesterol, producing the characteristic foam cells which are fat-containing histiocytes. It has been indicated, too, that patients with multiple eosinophilic granuloma of bone may develop the Schüller-Christian's syndrome should the base of the skull and hypophyseal region become involved.

Our second case represents an inflammatory histiocytosis predominantly of the Letterer-Siwe's type.

Case II. The patient, a twenty-one year old white male, was admitted because of progressive weakness of the lower extremities. In 1944, he noted a lump in the right groin which became painful in May, at which time a lymph node was removed and a diagnosis of Hodgkin's disease was made. A subsequent lymph node biopsy, prior to admission here, was reported as Boeck's sarcoid. He was discharged from the Navy in March, 1945, and then developed swelling and progressive weakness of the right lower extremity associated with pain in the right thigh and knee.

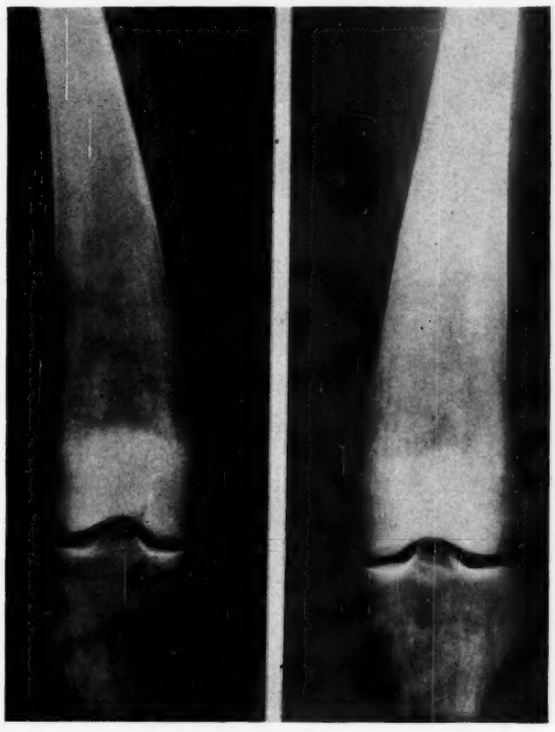


Fig. 1. Case I. Femurs in Gaucher's disease. Note characteristic Erlenmeyer flask appearance of lower halves with widening of the shaft.

Examination on admission revealed a young white male who appeared poorly nourished and chronically ill. There was a bony defect measuring 2 by 2 cm. in the left posterior parietal region of the skull. There was dullness over the right lower chest and fine râles were heard scattered throughout both lung fields. Lymph nodes were described as egg-sized in the left inguinal region and pea-sized in the cervical chains and both axillae. There was spastic paralysis of the right leg. A fine, pink, maculopapular rash over the lower chest and abdomen was noted. All sputa were negative for tubercle bacilli. Blood calcium was 9.9, phosphorus 4.5. Blood cholesterol varied between 134 to 223.

* Thannhauser[1] believes Schüller-Christian's syndrome to be a normocholesteremic xanthomatosis.

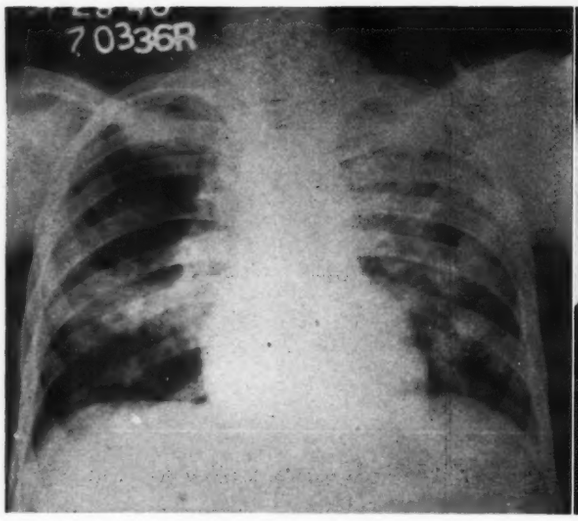


FIG. 2. Case II. Letterer-Siwe's disease. X-ray of chest showing mottled infiltration and honeycombing.

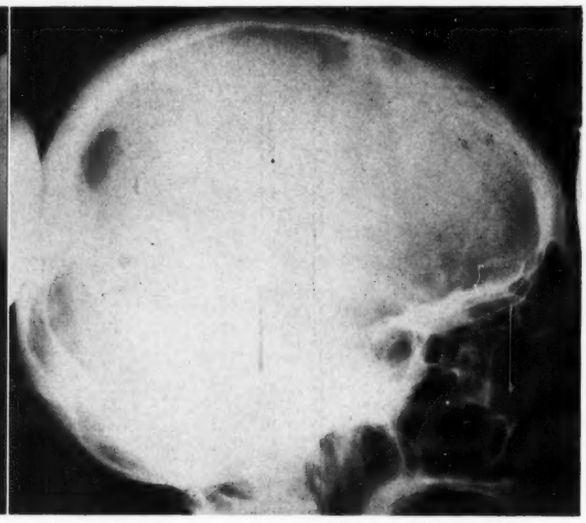


FIG. 3. Case II. X-ray of skull with bony defect involving inner and outer table of left parietal bone.

Acid and alkaline phosphatase were normal. X-ray of the chest showed a mottled infiltration and honeycombing of the upper one-third of the left lung and the paracardiac portion of the

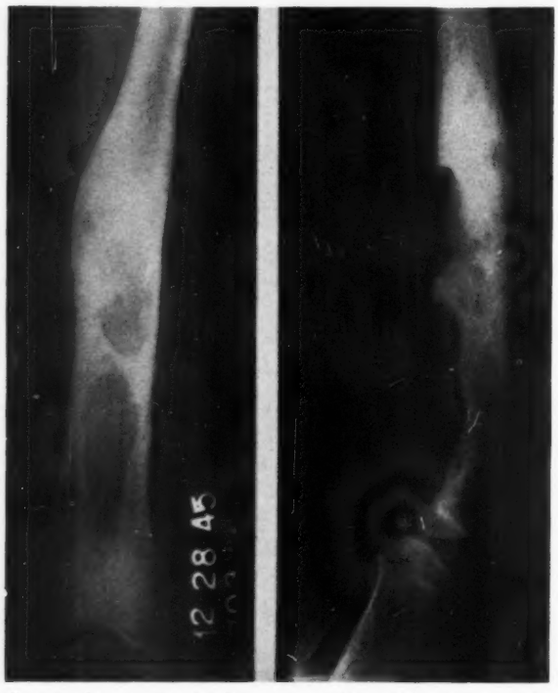


FIG. 4. Case II. Right femur revealing deformity, cystic lesions and expansion of shaft.

right lung. There was anterior wedging and collapse of the ninth dorsal vertebrae. The bodies of the seventh and the tenth dorsal vertebrae were moth-eaten in appearance. The skull showed a bony defect, 7 cm. in diameter, involving the left parietal bone. The lower half of the right femur revealed cystic, destructive areas with expansion of the shaft. (Figs. 2, 3 and 4.)

Biopsy of an axillary node on September 5, 1945 revealed lipoid histiocytosis. Slides received from the U. S. Naval Hospital of tissue taken from the right inguinal region in May, 1944 were interpreted as non-lipoid histiocytosis.

A plaster body-jacket was applied and the patient was given irradiation to the dorsal spine, left parietal region and right femur. The spastic paralysis of the right leg disappeared and the cranial defect diminished in size to 0.5 cm. in diameter. At the time of discharge on August 21, 1946, he was asymptomatic except for mild attacks of unsteadiness of gait. He appeared chronically ill. There were a few shotty lymph nodes in the cervical, axillary and inguinal regions. The chest was emphysematous and there was slight dullness at both apices. No râles were heard. The skin was dry and scaly and had a slight brownish discoloration. The last roentgenogram showed slight progression of the pulmonary infiltration. There was a definite decrease in the parietal defect of the calvarium although new, smaller areas had appeared.

As illustrated in this patient a biopsy of a fresh lesion reveals the granulomatous process but little or no lipoid material. Deposition of cholesterol occurs only with progress of the disease. Lipidization takes place with chronicity. The term non-

lipoid histiocytosis is therefore a misnomer. While the prognosis in the acute cases occurring in infants is poor, in the chronic cases seen in older individuals it is better and our patient appears to be doing fairly well.

Eosinophilic granuloma of bone originally was described as a solitary lesion in 1940. Later Jaffe and Lichtenstein,[2] Otani and Ehrlich[3] and Farber[5] described multiple involvement of bone with the same histiocytic pathologic entity. Characteristically, there are sheet-like collections of histiocytes some of which show phagocytic activity and among which are prominent numbers of eosinophilic cells, especially eosinophilic leukocytes. There are also fields of hemorrhage and necrosis and numbers of multinuclear giant cells some of which exhibit phagocytic activity. It is seen mainly in children and young adults. Almost any bone may be involved, most frequently those of the vault of the cranium, the ribs, the vertebrae and the long bones, especially the humerus and femur. Symptoms, when they occur, are local. They consist of pain and tenderness at the site of the lesion. There may be a leukocytosis or a slight eosinophilia. The blood cholesterol, cholesterol esters and alkaline phosphatase are usually normal. Roentgenographically, the bone involvement appears as a small or large radiolucent zone. In the calvarium the defects are circular and sharply delineated or punched out. The lesion may show expansion of the cortex and there may be pathologic fractures. The similarity to myeloma, Ewing's tumor and metastatic cancer is emphasized.

The course is benign; the prognosis is good. Treatment consists of small doses of x-ray or curettage. The lesions may resolve spontaneously.

Our third patient is a case of solitary eosinophilic granuloma of bone.

CASE III. The patient, a twenty-six year old veteran, was admitted October 23, 1945. In August, 1945, he began to complain of severe pain in the left side of his head.

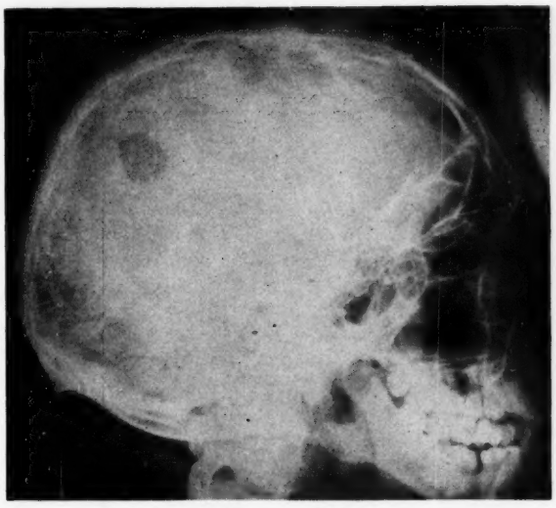


FIG. 5. Case III. Solitary eosinophilic granuloma of bone. Note sharply defined area of cystic bone destruction in left parietal bone.

Examination disclosed an area of softening of the skull in the left temporoparietal region, approximately 2 cm. in diameter. It was somewhat tender. Neurologic examination was normal. The remainder of the physical examination was negative.

X-ray examination of the skull revealed a 2 cm. in diameter, circular area of cystic bone destruction, sharply defined, in the left parietal region. This was surrounded by a faint, poorly defined zone of increased bone density. Both the outer and inner tables showed evidence of bone destruction. (Fig. 5.) The dorsolumbar spine, pelvis, chest, humeri and feet showed no abnormalities. The blood cholesterol was 286. Acid phosphatase was 3.0 and alkaline phosphatase 7.4 (King-Armstrong units). Operation showed a sharply defined, circular tumor in the left parietal bone near its prominence which was soft and grayish-yellow in color. This had destroyed the entire thickness of the table. Only the overlying periosteum was present.

Histologic examination showed a large number of eosinophiles. There were also histiocytes present, some of which were multinucleated and some of the histiocytes contained eosinophilic pigment. Most of the eosinophiles were of the multinuclear variety although an occasional one was of the mononuclear type. The diagnosis was eosinophilic granuloma of bone.

Following administration of 1,500 roentgens (in air) to the lesion, the patient showed considerable symptomatic improvement. His headaches disappeared. There was no evidence noted

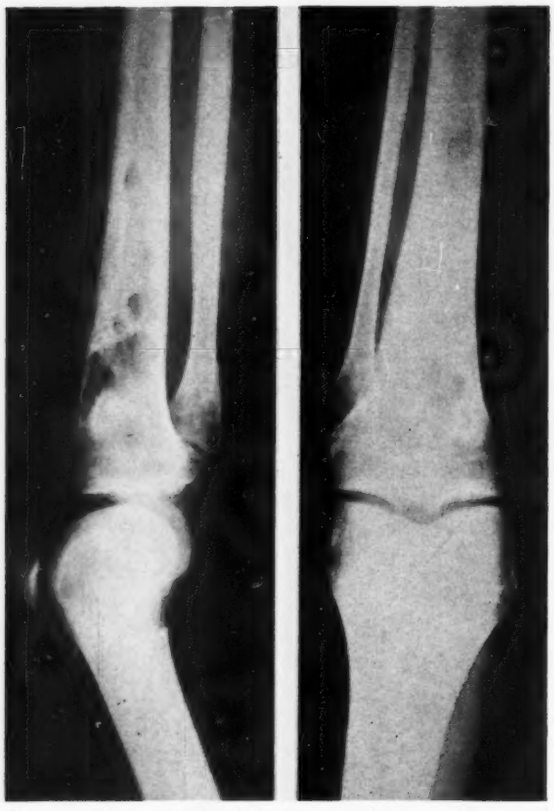


FIG. 6. Case IV. Multiple eosinophilic granuloma of bone. Cystic areas in distal portion of femur and proximal portion of tibia and fibula.

of regression of the skull defect, but there was blurring of the margins and the appearance of a thin outline of bone 2 mm. in width. The patient was afebrile throughout his stay. He was discharged December 12, 1945.

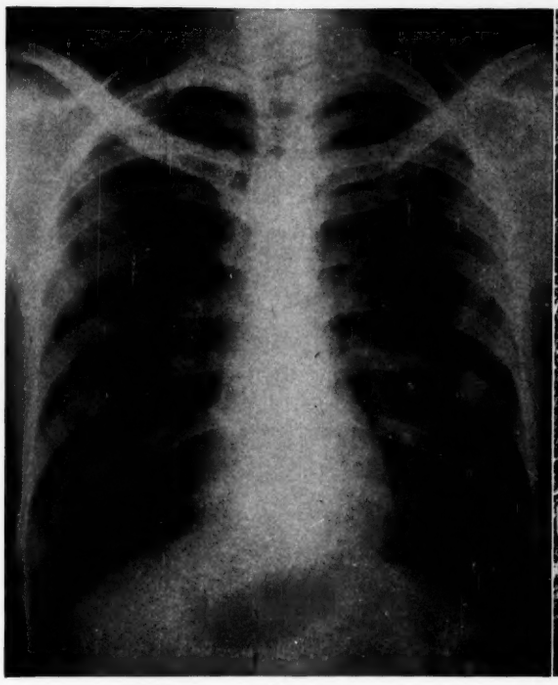
It has been emphasized in the literature[2–5] that eosinophilic granuloma of bone, as the name implies, is limited to the skeleton. Indeed, cases with visceral involvement have not been reported to my knowledge.[6]* The last patient, illustrating multiple eosinophilic granuloma of bone and also pulmonary infiltration presumably by the granulomatous process, is therefore of special interest. It also substantiates the essential identity of the three manifestations of inflammatory histiocytosis under discussion since visceral involvement is characteristic of Letterer-Siwe's disease and Schüller-Christian's disease. It will be recalled that our second patient with atypical Letterer-Siwe's disease exhibited the characteristic honeycombing or mottled involvement of the lungs.

CASE IV. A twenty-two year old white male was admitted on February 27, 1946. The patient was in fairly good health until November 14, 1944, when he entered an army hospital because of trench feet. On December 22, 1944, in the Dental Clinic, a cyst of the mandible was found. Prior to going overseas he had the two lower incisors extracted because they were loose in their sockets. The sockets never seemed to heal. Early in February, 1945, he noted pain in both thighs which was intermittent in character and lasted only several minutes at a time. There was tenderness of the thighs. Blood count on one occasion revealed 4 per cent eosinophiles. Biopsy of the right clavicle was reported as eosinophilic granuloma and was confirmed by the Army Institute of Pathology. The patient received a total of 10,200 roentgens through nine ports. Following this, he improved greatly. The bony defect disappeared, his appetite improved and he acquired more strength. In August, 1945, he had an evening fever which was unexplained and thought to be due to his disease. Final diagnoses were eosinophilic granuloma involving the skull, mandible, right clavicle, right and left radii and right and left femora.

On examination at this hospital, the patient appeared thin, somewhat undernourished and was ambulatory. The lower jaw was edentulous. There was a defect of the middle two-thirds of each mandible. A circular postoperative scar was present over the right clavicle. There was no lymphadenopathy. The chest was negative. Blood pressure was 104/70. The liver and spleen were not palpable. There was tenderness over the proximal portion of the right tibia. There was no swelling or depression. There was a defect over the middle two-thirds of the anterior surface of the right clavicle.

X-rays showed numerous punched out, clearly defined areas of decreased density over both frontal and occipital bones. The right forearm showed oval shaped areas of decreased density measuring 2.0 cm. in greatest diameter in the proximal one-third of the radius. Several areas of decreased density were noted in the mid-portion of the shaft of the left humerus, the distal portions of both femurs and proximal portion of the tibias. (Fig. 6.) Several areas of decreased density were noted in the upper one-third of the radius and ulna. The chest showed that the lung markings were exaggerated

* Since submission of this paper for publication, a case of eosinophilic granuloma of bone with multiple lesions of bone and pulmonary infiltration has been reported.[7]



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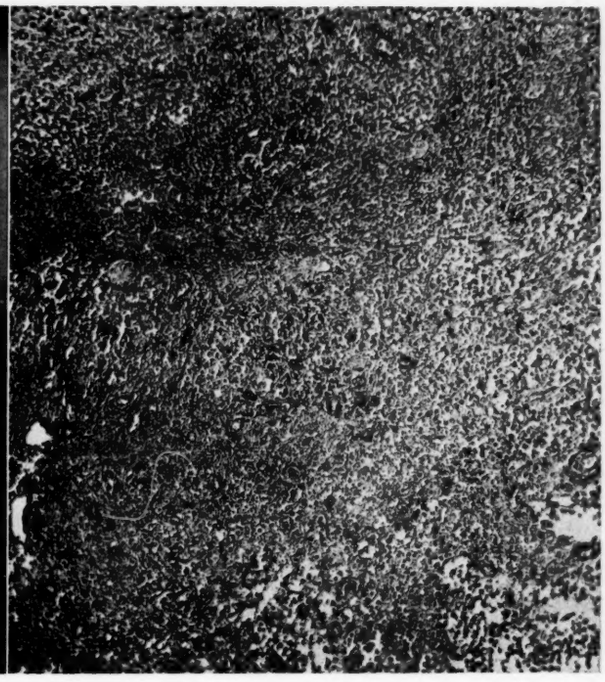

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FIG. 7. Case IV. Fine mottled infiltrations involving both lung fields.
FIG. 8. Case IV. Section from left tibia seen under low power. The light-staining cells are histiocytes. The dark-staining cells are eosinophiles. Note the presence of giant cells.

due to fine infiltrations occupying the entire left lung and the upper two-thirds of the right lung. X-ray findings were interpreted as changes in bones and lungs due to lipoid granulomatosis. (Fig. 7.)

The alkaline and acid phosphatase were 4.8 and 2.4. Sedimentation index was 17. Calcium and phosphorus, urea nitrogen and blood sugar were normal. Blood count was normal. There were 1 per cent eosinophiles present. There was no Bence-Jones protein in the urine. Biopsy from the upper third of the left tibia was reported as eosinophilic granuloma. (Fig. 8.)

The patient was given radiotherapy and was discharged on July 4, 1946 asymptomatic and in good condition.

CONCLUSIONS

It appears clear that eosinophilic granuloma of bone and its congeners, Hand-Schüller-Christian's disease and Letterer-Siwe's disease, represent merging clinical variations of an essentially similar pathologic process, best described collectively by the term inflammatory histiocytosis. These syndromes or entities are believed to be due to some obscure infectious process and produce a secondary disorder of the lipid metabolism. They are to be clearly differentiated from the primary lipoid metabolic disorders, Gaucher's and Niemann-Pick's diseases. Knowledge of these conditions will obviate confusion with malignant tumors involving bone and other granulomas such as tuberculosis and syphilis.

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Cor Pulmonale*

Observations on Forty-two Autopsied Patients

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Cor pulmonale constitutes one of the less common types of heart disease. Although recognized as a distinct entity, there is some difference of opinion as to the rôle played by chronic lung disease in its etiology.

The older concept was that the narrowing and thrombosis of pulmonary capillaries in emphysema elevated the blood pressure in the pulmonary circuit and thus put a strain on the right ventricle, which underwent dilatation and hypertrophy, and finally failed. Certain studies carried out in the past twenty years seemed to indicate that chronic lung disease does not produce cor pulmonale; but investigations of the last ten years herald a return to the older theory that chronic lung disease plays a definite part in its etiology.

Kountz and Alexander have followed this change in view, at first rejecting a connection between chronic lung disease and cor pulmonale, and later returning to the older viewpoint. In 1927 Alexander, Luten and Kountz[1] said "As a rule the heart remains free from injury after continuous bronchial asthma despite the attendant emphysema." In 1929 Kountz, Alexander and Dowell[2] wrote "It is believed that despite peripheral signs which simulate cardiac decompensation, advanced emphysema does not necessarily affect the heart." In 1934 Kountz and Alexander[3] presented experimental evidence showing that emphysema alone does not cause hypertrophy of the right heart, but in 1936 Kountz, Alexander and Prinzmetal[4] came to somewhat different conclusions. They maintained that the heart *is* affected in the majority of patients with emphysema and that there is experimental evidence that right ventricular dilatation and hypertrophy occur chiefly in the earlier phases of emphysema rather than in the later stages.

Other workers question a relationship between cor pulmonale and chronic lung disease. White and Brenner[5] said "Ordinarily, asthma, emphysema and pulmonary tuberculosis, even though of high degree, do not produce cor pulmonale." In 1936 Rubin[6] stated that in the absence of associated cardiovascular disease a selective or preponderant enlargement of the right ventricle in emphysema is an uncommon finding. In 1937 Parkinson and Hoyle[7] said "Cardiac failure from emphysema alone is surprisingly rare."

More recent work refutes this. For example, Griggs, Coggin and Evans[8] concluded that chronic pulmonary disease is an important cause of cor pulmonale. They found that right ventricular hypertrophy occurred in 54 per cent of patients with pneumoconiosis without other pulmonary or cardiac disease. They found that right ventricular hypertrophy occurred in 29 per cent of the patients with emphysema. Parker[9] found that in a high percentage of cases emphysema leads to ultimate failure of the heart. He also concluded that the severity of emphysema was closely related to the extent of right ventricular enlargement. Scott and Garvin[10] stated that the right ventricle is burdened in emphysema, presumably by an elevation in pulmonary pressure, and that it undergoes dilatation and hypertrophy and ultimately fails. Hallock and Rigler[11] concluded that chronic pulmonary disease is an important cause of cor pulmonale and subsequent heart failure.

* From the Department of Laboratories of the Jewish Hospital of Brooklyn.

Schiller, Colmes and Davis[12] stated that cor pulmonale due to chronic bronchial asthma is a more common disorder than is generally recognized. In discussing their series of cases of cor pulmonale, Spain and Handler[13] concluded that diffuse obstructive emphysema was the underlying significant pulmonary factor in the vast majority of cases. In the light of the conflicting conclusions just mentioned, it would seem that further study of this subject is indicated.

This paper deals with observations on

TABLE I
CASES OF COR PULMONALE

Comparative Data	Spatt and Grayzel	Spain and Handler[13]	Scott and Garvin[10]
Number autopsied cases	42	60	50
Criterion for diagnosis	Right ventricular wall averaging 5 mm. or more in thickness	same	same
Sex	32 males (76%) 10 females (24%)	56 males (93%) 4 females (7%)	48 males (96%) 2 females (4%)
Peak age incidence	51–70 yr.	50–65 yr.	Majority over 50 yr. of age
Peak incidence of heart weight	300–450 Gm. Average weight 401 Gm.	Average weight 460 Gm.*	400–500 Gm.
Thickness of right ventricular wall	36 cases (86%) 5–8 mm. 5 cases (12%) 9–11 mm. 1 case (2%) 20 mm. Average 7 mm.	Average thickness of right ventricular wall 8 mm. with extremes of 6 and 14 mm.†	41 cases (82%) 5–8 mm. 3 cases (5%) 10 mm. 2 cases (3%) 9 mm. 2 cases (3%) 12 mm. 1 case (2%) 11 mm. 1 case (2%) 14 mm.
Associated pulmonary disease	Emphysema, 29 cases; bronchiectasis and lung abscesses, 7 cases; pulmonary tuberculosis, 3 cases; carcinomatosis, 2 cases; pulmonary arteriolar sclerosis, 1 case	Emphysema, 40 cases; bronchiectasis, 6 cases; bronchial asthma, 6 cases; silicotuberculosis, 3 cases; pulmonary tuberculosis, 2 cases; kyphoscoliosis, 1 case; pulmonary arteriolar sclerosis, 1 case; organized pulmonary thrombi, 1 case	Emphysema, 32 cases; emphysema with conglomerulate silicosis, 7 cases; emphysema with ulcerative tuberculosis, 5 cases; emphysema with fibroid tuberculosis, 1 case; emphysema with silicotuberculosis, 1 case; conglomerate silicosis, 1 case; pulmonary fibrosis, 1 case
Symptoms	Exertional dyspnea, cough and cyanosis in most patients over a long period of time; venous distention, hepatomegaly, edema, and ascites less frequent and of shorter duration	Most patients complained of dyspnea suddenly getting worse; also, hemoptysis and cyanosis; later they had engorged veins, hepatomegaly, edema and increased venous pressure	Cough, exertional dyspnea and cyanosis were usual long-standing complaints; venous distention, hepatomegaly, edema and ascites rarely lasted longer than 6 to 8 mo.
Red blood cell count	Of 23 cases, when red blood count was available, 9 cases (39%) had a count of over 5,000,000; the highest was 7,560,000	Extremes of red blood cell count 3,300,000 to 6,500,000; average count, 4,960,000†	In 21 of 32 cases (66%) the red cell count was more than 5,000,000; the highest was 7,900,000

* Only average weight reported in this instance.
† Only average and extremes of thickness recorded.
‡ Percentage of cases with over 5,000,000 red cell count not recorded.

forty-two cases of cor pulmonale collected from the autopsy records of the Jewish Hospital of Brooklyn. These cases were chosen after elimination of all instances with valvular disease of the heart, those with more than minimal coronary sclerosis, those with clinical hypertension and all congenital lesions and luetic cardiovascular disease. (Table I.)

TABLE II

Disease	No. of Cases
Emphysema	29
Bronchiectasis and lung abscess	7
Pulmonary tuberculosis	3
Carcinoma with lymphangitic spread (carcinomatosis)	2
Pulmonary arteriolar sclerosis (marked)	1

It is recognized by various workers in the field that the best postmortem criterion for diagnosis of cor pulmonale is the separate weight of each ventricle. However, this information is rarely obtained. The authors have adopted the next best criterion, that used by other workers in the field,[8,10,13,14] a right ventricular wall averaging 5 mm. or more in thickness.

Of the forty-two cases observed, thirty-two (76 per cent) were males and ten (24 per cent) were females. The average age at time of death in the series was fifty-eight years; in the males sixty years and in the females fifty-three years. The largest group of patients (twenty-five cases) were between fifty-one and seventy years of age.

The weight of the hearts in the females varied from 250 to 340 Gm. and averaged 300 Gm. In the males they varied from 300 to 600 Gm. and averaged 401 Gm. Sixty-five per cent of the hearts weighed between 300 and 450 Gm. (twenty-seven cases).

In thirty-six cases (85.7 per cent) the thickness of the right ventricular wall varied between 5 and 8 mm. In five cases (11.9 per cent) the right ventricular wall varied between 9 and 11 mm; in one case (2.3 per cent) it was 20 mm. thick. Varying grades of left ventricular hypertrophy were seen. In ten cases (24 per cent) the left ventricular wall averaged 15 mm. or over in thickness. There was no strict correlation between the thickness of the two ventricles.

All the patients had some form of chronic lung disease, as seen in Table II.

Many of the patients with emphysema showed accompanying changes such as bronchiectasis, mild pulmonary artery sclerosis, fibrosis of the lungs and pleural adhesions. In two cases of emphysema there were marked degrees of kyphoscoliosis.

Of thirty patients in whom complete clinical histories were available, twenty-five complained of exertional dyspnea and of these, twenty noted this symptom for many years. Of these thirty patients, nineteen complained of chronic cough, with or without expectoration, over a long period of time. Cyanosis was slightly less frequent; it was present in seventeen cases. Edema, ascites, distention of neck veins, hepatomegaly and precordial distress were of much shorter duration than the former group of symptoms. Eight of these thirty patients had a history of bronchial asthma for periods varying from seven to fifty years, averaging twenty-six years.

Many of the patients in this series died shortly after entering the hospital so that no laboratory data are available except in twenty-three cases. In those patients in whom a red blood count was recorded nine (39 per cent) had a red cell count of over 5,000,000; the highest was 7,560,000.

COMMENTS

The conflicting opinions on various phases of cor pulmonale expressed by different workers may be due to the different criteria used in diagnosing cor pulmonale, and also to the fact that no attempt has been made to evaluate the variations in the dimensions and weight of the heart relative to body size, weight and sex.

The mechanism of dilatation and hypertrophy of the right ventricle seems fairly generally agreed upon. The pulmonary changes destroy and narrow blood capillaries in the lungs, causing pulmonary hypertension, which in turn increases the strain on the right heart thus resulting in dilatation and hypertrophy.

There are different explanations for the

accompanying left ventricular hypertrophy in some cases. Some workers believe that the anatomic relationship of the two ventricles is so intimate that hypertrophy of one chamber ultimately involves the other. Others believe that the accompanying left ventricular hypertrophy is due to the anoxemia which occurs in cor pulmonale. Still others maintain that the cause of left ventricular hypertrophy is as yet undetermined. The authors believe that both factors mentioned above contribute to left ventricular hypertrophy.

CONCLUSIONS

The data collected in this series of cases support the theory that chronic pulmonary disease plays an important rôle in the etiology of cor pulmonale.

Cor pulmonale is much more common in males than in females. Death in cor pulmonale occurs most frequently between the ages of fifty-one to seventy. At death the average age of the females in our series was seven years less than in the males.

Long-standing symptoms of exertional dyspnea, cough and cyanosis (indications of pulmonary disease) evidently reflect the first stage of the process. These are frequently followed by distention of the neck veins, hepatomegaly, edema, ascites and precordial distress (indications of the heart disease). The latter symptoms of heart involvement are of much shorter duration than the indications of pulmonary disease.

In over one-third of the patients (39 per cent) the red blood cell count was over 5,000,000.

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Review

Urinary Calculi*

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THE past five years have brought forth new theories, new data and new technical methods for the treatment of urinary calculi. A review of the subject is presented herein.

COMPOSITION OF URINARY CALCULI

Calcium oxalate. This stone is by far the most common in this climate on the diet prevalent in the United States. It forms in neutral urine or in urines which are slightly alkaline or acid.

Calcium phosphate. This stone is often mixed with both magnesium and carbonate complexes and is the next most common stone; it forms in alkaline urine.

Uric acid. This stone forms in acid urine and is to be found in heavy meat eaters.

Cystine. This stone also forms in an acid medium; it is often familial and is sex-linked to the females. We have several families of cystine stone formers in which many members of the family have cystine stones.

Most stones are not pure but mixtures of the first three mentioned, with one compound or the other predominating. Oxalate stones are commonly small, dark, rough and hard. Calcium phosphate stones tend to be soft, whitish and chalky, often forming casts of the infected calyces or pelves in which they lie. Uric acid stones are usually small and may be of any color although classically they are golden yellow. Cystine stones are commonly staghorn shaped and have a waxy, almost translucent character. Most staghorn calculi are either calcium phosphate or, in rare cases, cystine.

A new development in calculus analysis is the application of geologic crystallographic methods of analysis to these stones. A well trained geologist after some practice can make an excellent estimate of the amount of each compound present in the stone.[1] The trouble with this method is that technicians cannot readily be trained in this art.

THEORIES OF STONE FORMATION

All stones start as a small nucleus. If this nucleus is exposed to an overconcentration of any of the urinary salts mentioned above, it will grow rapidly into a stone. A good deal is known about the causes and prevention of the hyperconcentrations of urinary salts that make for stones but it is not yet known why the nucleus forms in the first place. It is well known that urine contains a far greater concentration of crystalloids than could possibly be dissolved in any ordinary aqueous solution. Crystals are present in most urine samples yet the bulk of the crystalloids does not precipitate out about these crystals. This is, as yet, a poorly understood colloidal phenomenon which is under investigation by physical chemists and may be far more important in the explanation of the formation of calculi than any of the more mechanical factors which we will consider here.

Some of the newer concepts of the initiation of the nuclei of stones postulate pre-calculus lesions in the form of (1) calcium plaques which form on the renal papillae,[2] caused perhaps by the action of distant toxins or by local necrosis[3] or by phagocytized calcium from the convoluted renal tubules. Many substances are concentrated in the convoluted tubules where Mayo Clinic investigators[4] found small amounts of calcium in phagocytes which they postulate may be carried down to the region of the pelvic epithelium to form deposits which erode through to the pelvic wall.

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Randall has found many such lesions in large series of autopsies. (2) Inspissated crystalline plugs in the terminal collecting tubules are frequently seen in autopsied kidneys. This phenomenon is seen with sulfa drugs when a plug of crystals protrudes from the terminal collecting tubule onto the surface of the renal pyramid. (3) Lesions of the tubular epithelium involving tubular cell death and postmortem calcification, the cells then sloughing to form a nidus for a stone. We also see this sort of thing in sulfa drug damage to the kidneys when damaged epithelial cells in the walls of the tubules die and may become calcified.[3] When and if such precalculus lesions form as nuclei on the pelvic wall, they are adherent to the wall of the kidney, not lying free. Later, they may break off in the renal pelvis. It is well known that trauma plus infection will cause stones in the kidney[5] and Rosenow claims that infection alone may cause stone formation, especially if organisms from stone formers are used. If, in experimental animals, the infected kidney is damaged by a cauterizing electrode, a stone will form at once. Foreign bodies or ulcerations in the bladder will cause stones to form, perhaps due to differences in surface tension in the urinary tract, the epithelium normally being protected by its own coatings.

Figure 1 shows a bougie which was left in the bladder and became the center of a very large calculus.

The older concepts of a nidus of desquamated epithelium, of bacteria or of pus are looked upon with increasing doubt since such phenomena occur in non-stone formers all the time. Furthermore, such niduses have not been demonstrated by investigators who made serial sections of many stones. It is not known why foreign bodies become calcified in some people and not in others or why only segments of the foreign bodies become calcified.

Once the nucleus is formed any factor which increases the excretion of urinary salts will cause the stone to grow rapidly. The factors which increase the concentration of salts in the urine should be looked for in stone patients, since they may be corrected. They are as follows:

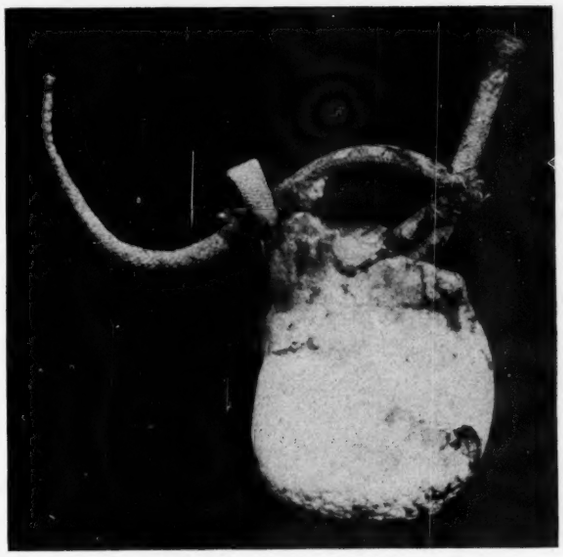

FIG. 1. A large bladder stone which formed around a foreign body (bougie) inserted into the bladder during an attempted abortion.

1. Stasis, which may be due to obstruction by the prostate gland, strictures of the urethra, ureteroceles, strictures of the ureteropelvic junctions or calyceal neck obstructions. These obstructions may be corrected surgically.

2. Bed immobilization, as in body casts or in chronic illnesses, will cause osteoporosis with hypercalcinuria which reaches its peak about a month after bed rest is started. These patients drink too little water if left to their own devices. An output of over 2,000 cc. a day must be maintained.

3. Infection of any kind in the urine will aid and abet calculus formation and if urea-splitting organisms such as Bacillus proteus or some of the staphylococci are present large quantities of ammonia are formed. The urine becomes strongly alkaline and is loaded with calcium salts.

4. Concentration of the urine, as by inadequate fluid intake or by excessive sweating. The Army Air Forces did a fine study of this aspect of the problem and found it most important in the formation of calculi in its members during the war.[6] The Air Force also conducted an excellent study on

the effect of warm climates and sweating upon calculus formation. They found that in the European Theater the incidence of kidney stones among the troops was 0.5 per thousand per year whereas in the warm climate of the China, Burma, India Theater and the Pacific Theater the incidence was 2.5 per thousand per year. In all areas where sweating was heavy, stone formation was prevalent. The flying personnel had a much greater incidence of calculi than the non-flying personnel. This was attributed to the fact that flyers were nervous, perspiring considerably as a result, and were often clothed in heavy flying clothing and flak suits during the take-off at warm, low levels during which time they perspired further. In addition, there was very little drinking water in aircraft which were on long trips and fluid intake was low. The type of diet did not influence the incidence of stones but did influence the type of stone which was formed. For instance, the flyers who partook heavily of iced tea, chocolate and greens formed oxalate stones whereas in the Navy the men formed uric acid stones because of their high meat diet.

5. Conditions which cause a hyperexcretion of calcium in the urine are: (1) Hyperparathyroidism. (2) Eating of large quantities of dairy products causes a transient hyperexcretion of calcium in some normal people and a pronounced unexplained hyperexcretion in most stone formers.[7] (3) Sippy regimens are to be avoided in known calculus-forming patients. (4) Large doses of vitamin D will cause a temporary hyperexcretion of calcium in the urine. (5) Long immobilization, as in fracture patients who are in body casts or in chronically bedridden patients who develop osteoporosis with hyperexcretion of calcium. (6) Marked vitamin A deficiencies appear to cause heavy phosphaturia and a persistently alkaline urine, in addition to epithelial ulcerations which rapidly become infected and encrusted. This work has been confirmed in experimental animals, not in the human.

6. Cystinuria is a familial disease in which the urine is loaded with cystine. This tendency seems to be sex-linked to the female. Hyperexcretion of xanthine is another such disease. These calculi form in acid urine but again calculi do not form in all patients with such hyperconcentration, only in 2 or 3 per cent of these patients. The cause of the origination of these stones is not known.

All of the lesions which we have described can be recognized and corrected. However, for every patient with a lesion that can be corrected there will be several others in whom nothing can be found to account for their being stone formers or to explain the aggravation of any incidental stones which they might have. There are, of course, known stone belts in the world. Florida and California, Central Russia, Indo-China and Syria are well known as stone districts, whether due to the hot climate or to certain peculiarities in the diet of the natives is not known. It is not related to the "hardness" of the drinking water or to geologic strata. In South Africa, for instance, an analysis of some 11,000 white patient admissions showed an incidence of 5 per cent renal calculi whereas a group of 1,000,000 negroes, living in the same area, showed no calculi at all. It was suggested that the negro diet was somewhat richer in vitamin A.[5] Certainly stones are more common among the cereal-eating groups of the world population.

SYMPTOMS

The classical symptoms of urinary calculi are attributed to three factors (1) Local trauma to the pelvis or ureteral wall by sharp spicules of stone which causes severe intermittent spasm or bleeding, and later erosion of the wall with infection and further bleeding. (2) Obstruction of the ureter. If this is acute, there is colic; if it is gradual, there is no pain as in the slow occlusion of the ureter by carcinoma. Both blockages lead to hydronephrosis. (3) Infection. The kidney is very vascular and the damming back of infected urine readily leads to septicemia with chills and fever. Admission

temperatures on the urologic service often run as high as 105°F.

Figure 2 shows a small stone less than 1 cm. in diameter which has fallen from the kidney down into the mid-ureter. This small stone blocked the ureter causing renal colic and extreme discomfort. Huge staghorn calculi which are much larger than this stone may cause no symptoms at all in the kidney. They lie silently in the kidney but erode the wall of the pelvis causing infection and frequency of urination with burning. It has been said that the kidney is an inarticulate organ but that the bladder speaks for it.[9]

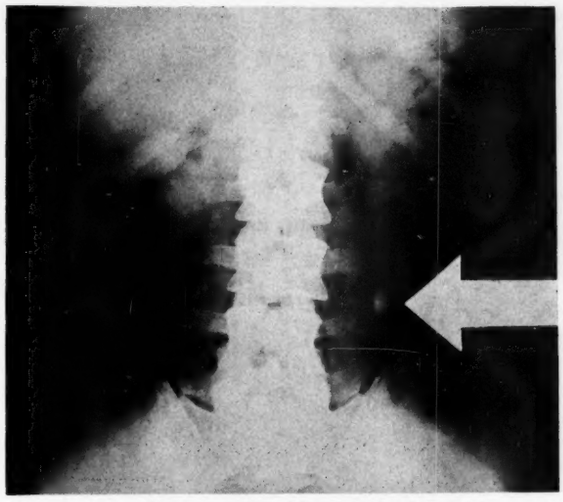

FIG. 2. A small stone which blocked the left mid-ureter causing severe colic.

DIAGNOSIS

Diagnosis of renal stones is not difficult. A history of urinary frequency, discomfort or hematuria is easily elicited. The pain distribution is suggestive, the urine is readily analyzed and x-rays show the stone. It is up to the doctor to make this diagnosis. Many plain films of the abdomen taken in emergency wards are technically poor and will not show small stones due to poor preparation of the patient, to feces or gas, or to hurried technic. Some 5 to 10 per cent of all stones are not opaque to the x-ray as in the case of the occasional pure uric acid stone.

If there is doubt about the plain x-ray, 20 cc. of diodrast is injected into the patient's vein and pictures are taken. Hydronephrosis and hydro-ureter may be caused by a stone which is so small and has so little density that it will not show in the initial x-rays.

A cystoscopic catheter will, of course, verify the existence, location and size of a suspected stone. An air pyelogram can be used for non-opaque stones. Good x-ray technic has made the wax-tipped bougie almost obsolete.

The differential diagnosis between urinary calculus and appendicitis or pelvic inflammatory disease is sometimes difficult because of the similar pain distribution. Rarely, cholecystitis may be confused with kidney disease. Cystoscopic and x-ray examinations will establish the diagnosis. Nevertheless, three fourths of the patients with right ureteral stones come to the hospital with a scar in the right lower quadrant, an indication that all too often an innocent appendix had been removed.

TREATMENT

If there is colic, morphine sulfate gr. $\frac{1}{4}$ (0.016 Gm.) and atropine gr. $\frac{1}{100}$ (0.6 mg.) are given. If this does not relieve the colic in one hour, the dose is repeated. For the second medication papaverine may be given intravenously in a dose of .03 Gm. to relax the ureter.

Strain the urine. The patient is instructed to urinate into a vessel through four thicknesses of gauze. The probable appearance of the stone is explained to him in detail. He is told to expect a hard fragment of the size indicated by the x-ray. It may be any color, black, white or yellow and it may be broken up into sand. It will never be as large as the patient anticipates. If this is not said, patients have a tendency to discard small stones as not measuring up to their expectations.

A culture is taken of the urine since infection is a prominent feature in these cases and chemotherapy will obscure any later cultures.

The patient's intake and output are measured and a blood urea nitrogen is

taken. One must be always on the alert for a calculus anuria wherein calculi on one side will, in an unexplained manner, cause the shut-down of both kidneys which may be most refractory to treatment. There have been four such patients in this hospital in the past fifteen years, three of whom died.

Urinalysis is ordered to include microscopic examination and a stained smear of the urinary sediment. A test with Sulkowitch reagent for excessive calcium excretion[10] should be done.

Chemotherapy appropriate for the organism found in the urine is started. Penicillin may be given up to 50,000 units every three hours intramuscularly; streptomycin up to ¼ Gm. every three hours for periods up to three weeks and sulfadiazine may be given if there is no blockage of the urinary tract. Sulfacetamide is particularly good in these cases in that no urinary alkalinization is required for this more soluble drug.

A serum calcium, phosphorus and alkaline phosphatase should be taken in every patient with stones and repeated at intervals to rule out hyperparathyroidism.

Antispasmodic Drugs. Depropanex, a pancreatic extract, has not helped our patients. Syntropan and trasentin appear to have some usefulness and a new drug called amethone is presented[11] as being particularly useful in renal colic. Actually, few of these drugs have served us as well as morphine and atropine. If high fever and pain persist, a cystoscopic catheter is passed up beyond the stone to provide drainage. After such a catheter has been in place for one or two days and the edema and infection have subsided the catheter may be removed and often the stone will pass within the next two or three days.

Cystoscopic Manipulation. The newer cystoscopes are considerably smaller than the caliber of the normal urethra and have a surprisingly large visual field inside the bladder. Small stones in the lower ureter may be removed (1) by introducing catheters into the ureter around the stone, after which the stone will pass, or (2) by introducing a stone-removing basket, a device of fine wires or catheters which are bowed out in such a manner that the little stones may fall in between the wires and thus be removed when the basket is withdrawn[12] and (3) by means of small rubber bags on the end of ureteral catheters which may be introduced up to the stone and the bags dilated to a caliber larger than the stone. Then, as the bag is withdrawn down the ureter beneath the stone, the stone may follow the bag out into the bladder.[13] Usually, small stones under 1 cm. in diameter will pass spontaneously, but they may take as long as two or three months and meanwhile infection and erosion of the ureter will occur. If stones are present in the bladder and have grown to a size of 2 cm., they will not pass through the urethra but can be broken up with a lithotrite, an instrument for crushing stones which are in the bladder. The operation of crushing stones this way is referred to as litholapaxy.

If the patient's stone is not amenable to any of these methods and is doing damage, it should be removed surgically. The approach to renal and upper ureteral stones is through the flank; for ureteral stones lodged below the brim of the pelvis the approach is through a para-inguinal or paramedian incision and for bladder stones the approach is suprapubic, down through the space of Retzius and into the bladder. All of these approaches are extraperitoneal. In removing multiple small kidney stones it is often difficult to locate all of the tiny fragments in the tips of calyces. Some of these are frequently left behind and then form the nuclei for new stones. A new technical development which is helpful in these instances is the fibrinogen-thrombin coagulum which has been worked out at Duke University[14] for injection into the exposed renal pelvis at operation. After four minutes this coagulum becomes twenty times as tough as an ordinary clot, and after it has solidified a larger incision is made in the pelvis and the coagulum is withdrawn, carrying with it the tiniest stones which might otherwise have been left behind. At this writing the coagulum is not yet on the commercial market.

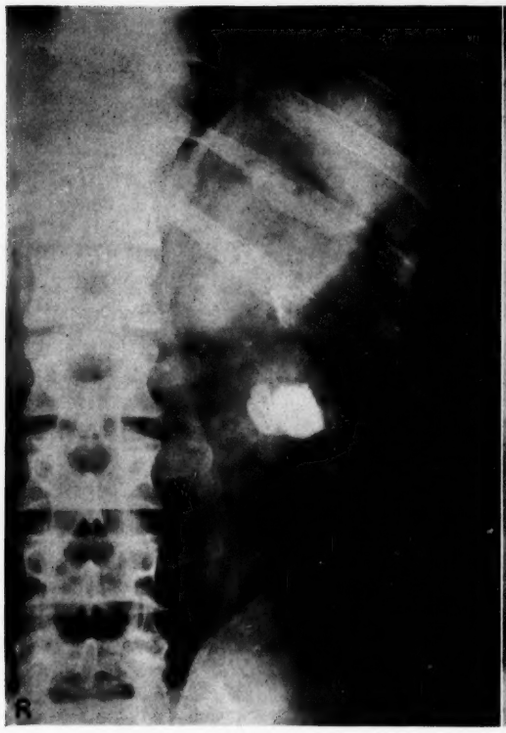

FIG. 3. Left renal calculi before irrigation with Suby's stone-dissolving solution introduced through a nephrostomy tube.

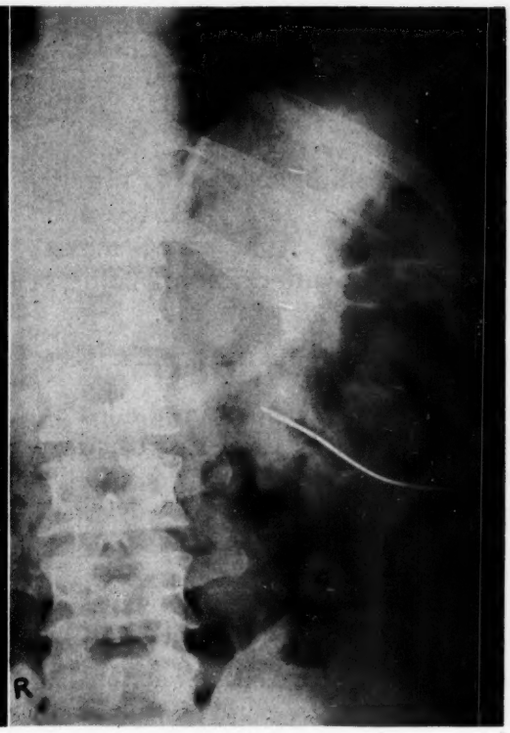

FIG. 4. The same patient after twenty days of irrigation. Suby's solution caused the stones to crumble and they were lifted out through the nephrostomy opening.

Stone-dissolving Solutions. The current status of stone-dissolving solutions is developmental. They are citric acid solutions which have been buffered with magnesium oxide and bicarbonate to make them less irritating. They can be used on the occasional large, soft, calcium phosphate stones. They are also useful against alkaline-encrusted cystitis lesions in the bladder. They are useless against the more frequent hard stones, such as the calcium oxalate kidney stones or the usual hard bladder stones. The chief drawbacks to their use are the difficulties in application of the solution to the stones. A tube must be maintained in the kidney for periods up to three weeks in order that the stones can be continually washed with the solution. A tube must be kept either in the ureter or in through the flank for this period. If the stones do not loosen or crumble within three weeks, the interior of the kidney may become irritated by these strong solutions. The solutions are being developed further by Dr. Fuller Albright, Dr. Suby and their group in Boston.[15] Rarely do these solutions dissolve a stone completely although now and then a spectacular result is obtained.

Suby's solution was helpful in the following case: Figure 3 is the x-ray of a patient who was irrigated through a nephrostomy tube. It is apparent that at the end of twenty days (Fig. 4) all of his large laminated calculi were gone. These stones, however, did not dissolve but merely became loosened and softened to such an extent that they fell into the nephrostomy tract and could be grasped with a Kelly clamp. Suby's solution is often used in tidal drainage apparatus for paraplegic patients to prevent bladder concretion.

Can stones be dissolved by diet? Yes, they can be, but very rarely. Cystine stones, if pure, will sometimes dissolve in a strongly alkaline urine after many weeks. It has been argued by Higgins[5] that many alkaline stones will dissolve on an acid-ash diet. However, acid-ash diets may, in truth, cause

an increase in the amount of calcium available in the urine for stone formation. They are relatively ineffectual in lowering the pH of the urine, especially in the presence of infection. It is so much easier for the patient to take ammonium chloride or nitrate that acid-ash diets are being used less and less. The ease with which these medications can throw a patient with damaged kidneys into acidosis must be kept in mind.

PREVENTION OF RECURRENCES

Dilution of the urine is first on the list of preventive measures. All stone patients are instructed to drink 3 quarts of water daily. If the patient is a paraplegic or is bedridden with a fracture, the intake is raised to over 4 quarts per day. A diet is prescribed which is low in the elements from which the stone was formed. In addition, transitory showers of hyperexcretion of these elements must be prevented. For instance, patients who have had stones which contained calcium are cautioned not to drink large quantities of milk or fruit juice at any single meal. Instead, they should take small amounts at long intervals.

Obstructions in the urinary tract are removed. Ureteropelvic junctions are carefully studied for obstructions that can be corrected and renal ptosis is remedied if it is severe. Ureteroceles are opened and bladder neck obstructions or strictures are removed.

Urinary tract infection which is so often present is now attacked vigorously according to the organism found upon culture. Streptomycin and penicillin are given in adequate doses. Sulfacetamide is particularly useful because of its ready solubility but leukopenia and anemia must be guarded against. Mixed chemotherapy is becoming increasingly versatile and effective and when it is combined with improved drainage much can be accomplished.

The patient's blood calcium and phosphorus are checked repeatedly since early in the disease only low phosphorus may be found. It must be borne in mind that if hyperparathyroid patients develop renal damage, as they so often do, they may go into uremia; whereupon the blood phosphorus will rise and the blood calcium will come down, sometimes to relatively normal values. It is therefore important that the blood urea nitrogen be determined in all these patients. Parathyroid tumors are removed if they are present. A high calcium intake given after parathyroidectomy in order to replace the bone damage may cause renal calculi to reform unless precautions are taken. The urine must be kept very dilute and clear of infection and obstruction.

To prevent stasis in patients who are immobilized in bed or in casts for long periods of time, change their position frequently, force fluids and keep their urine clear and acid. All stone patients are x-rayed at one, two, three, six and twelve months after they have passed the stone. If the patients have had uric acid stones, they are kept on an alkaline-ash diet at least for a time; although if we assume that precalculus lesions are present, even in uric acid stone-forming patients, we might merely change the character of the stone from an acid stone to an alkaline stone. If the blood uric acid is high, measures should be taken to keep the urine roughly neutral in reaction. If the patient is suspected of having a vitamin A deficiency, a photometric test is made. It is probably advisable to give vitamin A to all stone-forming patients in view of the present incompleteness of our knowledge as to the formation of stones even though this factor seems to be somewhat over-rated. Usually 100,000 units of vitamin A per day are prescribed. It is occasionally possible for a patient to bring to the laboratory some calculi which have been passed by other members of his family. These should be analyzed with an eye to possible familial factors such as cystinuria.

New research is currently under way which may make it easier to prevent certain stones from forming. It is known that the body maintains its calcium in the urine in solution partly through the elaboration of citric acid in the urine. It is also known that the administration of estrogenic hor-

mones will increase the citric acid output. It was therefore suggested by Dr. Shorr[16] of New York Hospital that if one were to administer estrogens and at the same time administer aluminum hydroxide preparations in large doses (up to 160 cc. a day) in order to lower the excretion of phosphorus in the urine, one might hope to prevent further stones from forming in people who are known to form phosphate stones readily. No large series of cases on these regimens has been reported but two obstacles have already appeared. First, ordinary aluminum hydroxide preparations tend to make for constipation in these patients and may even cause intestinal obstruction. Magnesium trisilicate is now added to amphojel to counteract the constipation. Second, it has been revealed that other experimenters[17] use estrogens to cause stones in male rats and although they attribute the stone formation to stasis in the urinary tract, due to hypertrophy of the prostate and other tissues in male rats, this has nonetheless discouraged use of estrogens.

In 1937 a Danish worker, Hammersten,[18] suggested that a high magnesium intake was beneficial in the prevention of stones and might even bring about stone dissolution, at least in animals. This work is under investigation by Barrett.[19]

It is this type of research which is in progress today from which we hope to learn more and more practical methods for controlling calculus disease.

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Seminars on Protein Hydrolysates

Problems in the Evaluation of Protein Therapy*

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EVALUATION of the protein nutritional status is becoming increasingly important in medical and surgical practice. In spite of the availability of several excellent reviews[1,2] on the subject a number of misconceptions still prevail. A false feeling of security may result from erroneous conclusions drawn from fragmentary evidence. An anticipated response to a given type of protein therapy may not occur when special conditions interfere with normal protein metabolism.

In this paper an attempt will be made to review and to scrutinize the various factors to be considered in the evaluation of data relating to protein nutrition, and to analyze a number of peculiar situations that challenge the classical concepts of protein metabolism and, in practice, present pitfalls in the evaluation of protein therapy.

GENERAL CONCEPTS

Evaluation of the Protein Nutritional Status. The only tissue "biopsied" for evaluation of the protein nutritional status of the body is blood plasma. The assumption is often made that the concentration of plasma protein reflects the protein concentration of the body in general. That this is true in the dog has been shown by Weech[3] who demonstrated that the loss of tissue protein of the dog subjected to chronic protein depletion is paralleled by a loss of circulating albumin at a rate of 1 Gm. of albumin for 30 Gm. of tissue protein. One may assume that this relationship holds true in man in those rare instances in which one deals with simple protein starvation in the presence of adequate hydration. In most types of human hypoproteinemia, however, it is unlikely that the loss of circulating protein correctly reflects the general protein nutritional status. In instances of acute loss through hemorrhage or in burns this relationship does not prevail and relatively small amounts of plasma protein given intravenously may replete the protein deficit. In other special situations the total protein deficit may be considerably greater than would appear from the concentration of plasma protein.

The plasma protein concentration is affected by many variable factors which do not change the total circulating protein. Simple physical factors, such as changes in the patient's position, will alter the plasma volume. Hemoconcentration or hemodilution resulting from changes in the state of hydration of the patient may likewise rapidly alter the plasma volume and thereby change the plasma protein concentration.

For these reasons the practical value of the plasma protein determination is questionable in the majority of cases. There are chemical, methodological considerations which further impair the value of "total protein" that so often determines the clinician's decisions.

It has been found by Adams[4] that the falling drop method in copper sulfate as described by Phillips[5] and associates for the determination of plasma proteins, while fairly reliable within the normal range, is not accurate enough in the hypoproteinemic range. This same relationship has

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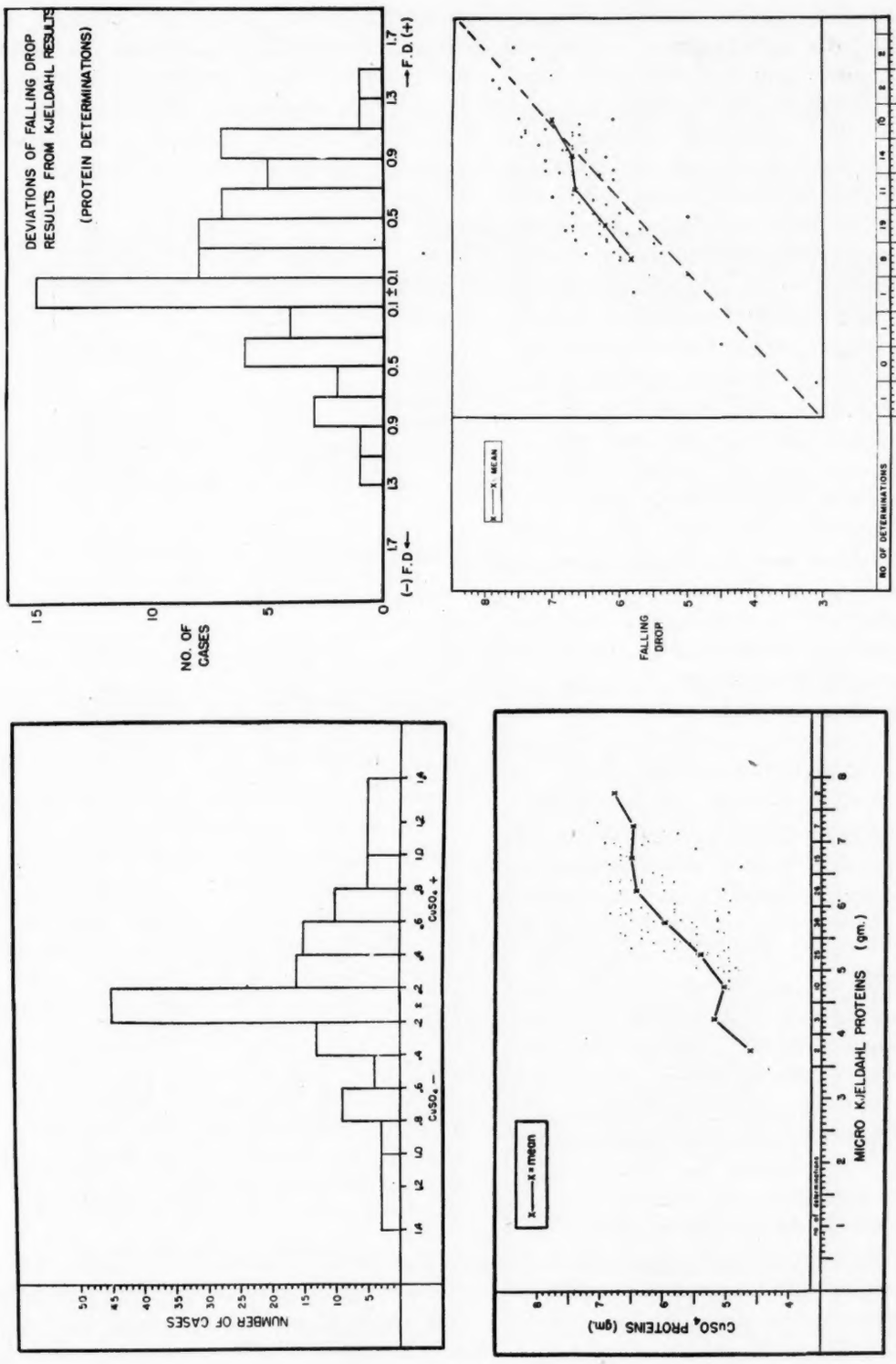

FIG. 1. Comparison between values of plasma protein concentration obtained by the Kjeldahl method and by methods making use of measurements of specific gravity (Phillips[5] on the left, Kagan[6] on the right). The charts on the left are reproduced from the paper by Adams et al.[4] (Through the courtesy of the *J. Lab. & Clin. Med.*, 31: 507–513, 1946.)

been encountered by other authors* (Fig. 1) in comparing the falling drop method of Kagan[6] with the values obtained for total proteins by the Kjeldahl method. For the present, only the Kjeldahl method as a measure of the nitrogen (corrected by the values obtained for non-protein nitrogen) will give an accurate estimation of plasma protein concentration. The methods most frequently employed by clinical laboratories for the rapid determination of the concentration of plasma proteins are intrinsically unsatisfactory in the range where they are most important for the evaluation of the patient's plasma protein concentration.

In addition to the total protein concentration one has to consider that various protein components may be selectively lowered or elevated. The use of a single figure to express the ratio of albumin to globulin is to be condemned as misleading and the values for each of these proteins should always be considered separately.[2]

Accurate determination of the plasma albumin concentration by salting out methods presents considerable difficulties. The most reproducible definition of plasma protein components today is by electrophoretic methods which separate the components by their specific mobility in an electric field. The salting out method of Howe[7] determines the "sodium sulfate soluble" albumin. This corresponds to the albumin and $\alpha_1 + \alpha_2$ globulin of the electrophoretic analysis. Salting out at different concentrations[8] may result in better duplication of the electrophoretic pattern. Provided the fractions obtained by the various salting out procedures are always the same, these methods are probably satisfactory.

It has been found by Petermann et al.[9] that under certain circumstances the "sodium sulfate soluble" albumin consists of more α_1 and α_2 globulin than ordinarily. Thus in patients with gastric cancer, for instance, the administration of a high protein diet may alter the solubility of α_1 and α_2 globulin in such a way as to make them more likely to appear as "albumin" in the Howe method. The "albumin" as measured by this latter method will increase and will create the impression that the therapy is effective, whereas actually, as shown by electrophoresis, the true albumin value may remain unchanged in the absence of any response to the therapy used. Alcohol precipitation in the cold[10] has been difficult to control and has not been reliable in our hands. A new method measuring the precipitate in serum formed by the addition of an animal antiserum prepared by immunizing the donor animal with human albumin has produced results in the hands of its author, Dr. B. F. Chow,[11,12] that compare favorably with electrophoretic results obtained in our laboratory on the same samples. (Table I.)

TABLE I

COMPARISON OF ANALYTICAL RESULTS OF HUMAN ALBUMIN IN SERA CONTAINING DIFFERENT AMOUNTS OF ELECTROPHORETIC ALBUMIN, WHICH IS TAKEN AS 100 PER CENT*

Albumin in Sera, Per Cent	Per Cent of Electrophoretic Albumin Found by		
	Precipitin Reaction	Salt Fractionation	Alcohol Precipitation
20–30	101 ± 4.0	195 ± 1.0	
30–40	102 ± 3.6	144 ± 5.2	135 ± 3.4
40–50	105 ± 2.7	142 ± 3.8	121 ± 3.6
50–60	106 ± 3.8	133 ± 1.9	120 ± 4.7

* From Chow, Homburger, DeBiase and Petermann.[12]

It may thus be hoped that simpler and more reliable methods will become available for the measurement of the albumin fraction of blood proteins.

SPECIAL CONSIDERATIONS

There are peculiar disturbances of protein metabolism which render the evaluation of the protein nutritional status even more difficult than it usually is. These may be classified into two groups.

Instances with High or Normal Plasma Protein in Spite of Tissue Depletion. The plasma protein concentration may show an ap-

* Unpublished observations by Trunnell, J. B. and Homburger, F. shown in Figure 1.

parent increase due to dehydration with a reduction of plasma volume. This situation occurs in surgical patients and in a number of conditions involving profuse sweating, ensuing hemoconcentration may mask a reduction of the total circulating protein.

Instances of Low Plasma Proteins Persisting at Hypoproteinemic Levels in Spite of Repletion

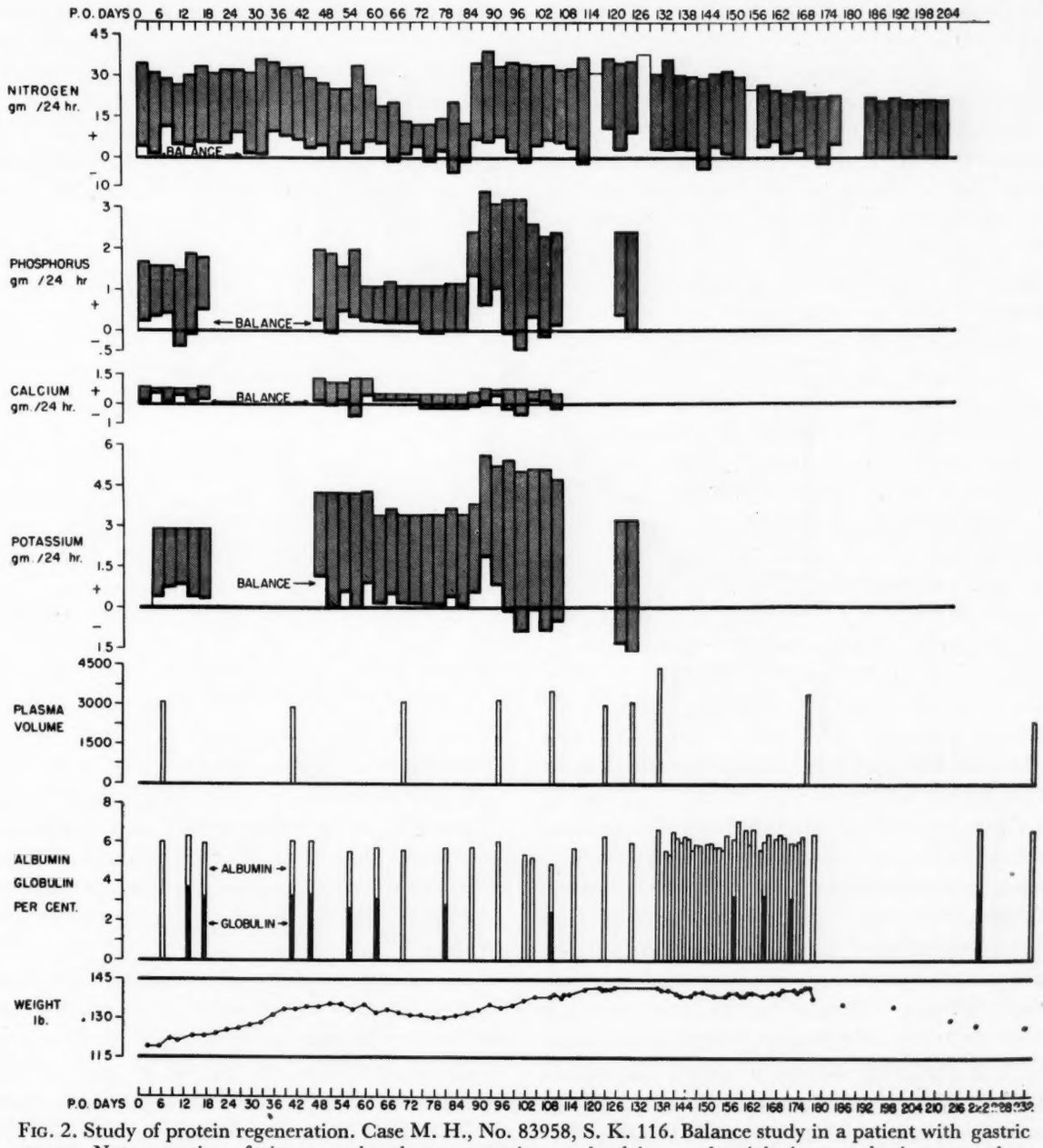

FIG. 2. Study of protein regeneration. Case M. H., No. 83958, S. K. 116. Balance study in a patient with gastric cancer. Note retention of nitrogen, phosphorus, potassium and calcium and weight increase lasting more than 150 days. Increase of circulating plasma protein occurs late and is only temporary, decreasing again with weight loss and reduction of plasma volume as tumor recurs. Patient died thirty-three weeks after study was completed.

elevated temperatures and/or prolonged diarrhea and vomiting. In cases of edema with fluid shifts into the extravascular space the reduction of the plasma volume and the

of Tissue Proteins. There are some disorders of protein metabolism which are characterized by a hypoproteinemia persistent in spite of a high protein intake with evidence

of protein regeneration in tissues other than blood. This has been described in certain types of kidney disease by Keutmann and Bassett[13] and in tuberculosis by Co Tui.[14]

In Figure 2 is shown a nitrogen balance study and electrophoretic analysis of plasma proteins together with studies on the plasma volume in a case of cancer of the stomach. In this case the patient had undergone partial gastrectomy eleven days before the study and died of recurrent carcinomatosis seven months after the study. It may be seen that fair amounts of nitrogen, potassium, calcium and phosphorus were retained throughout the long period of investigation. Yet no regeneration of plasma protein was observed and the albumin values remained exceedingly low throughout the study. There was a continuous weight gain that levelled out toward the end of the study when apparently the individual's general protein nutritional status became stabilized. After seven months of a high protein diet, regeneration of plasma protein finally took place. Curiously, this occurred at a time when there were signs of recurrence of the carcinoma, such as weight loss and weakness, thirty-three weeks before the patient's death from extensive abdominal carcinomatosis. It may be argued that the depletion of protein was so extreme in this case that unusually large amounts of protein were necessary to make up the loss and that plasma protein regeneration finally occurred as the general deficit was made up; but this seems unlikely in view of the clinical history indicating plasma protein repletion at the time of recurrent weight loss.

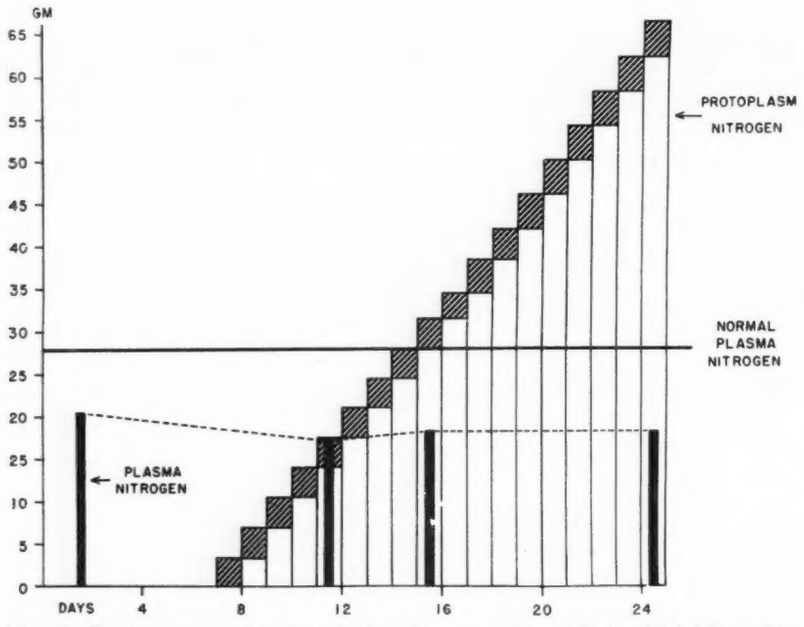

FIG. 3. Estimated protein distribution in a patient with familial idiopathic dysproteinemia.[15] Nitrogen retained during eighteen days' balance study (cross-hatched areas) is not utilized to increase plasma protein which has remained low while the patient remained on high protein intake during one year preceding this study.

In another case hypoproteinemia persisted for two years while the patient had a protein intake of at least 100 Gm. and maximally 200 Gm. per day without evidence of nitrogen loss in urine and feces. This situation prevailed in a case of idiopathic dysproteinemia.[15] The nitrogen distribution in this case is shown in Figure 3 during a period of nitrogen balance study carried on for eighteen days at the end of the first year of this patient's high protein intake. Again it is clear that in spite of nitrogen retention (accompanied by phos-

phorus and potassium retention) no regeneration of plasma protein occurred.

Finally, the postoperative phase in major surgical procedures presents a situation in which the condition of apparent eu- or hyperproteinemia may be seen caused by hemoconcentration and in which, conversely, intractable hypoproteinemia may also be encountered. The pathogenesis of the latter condition in such instances is entirely different from that prevailing in gastric cancer, idiopathic dysproteinemia, etc. It is the excessive nitrogen loss which in such examples of "alarm reaction" renders replacement of lost protein difficult. With forced protein feeding, using hydrolysates by mouth, jejunal tube and/or parenterally, positive nitrogen balance[16,17,18] and protein regeneration[19] can usually be obtained.

To achieve this at least 0.6 Gm. of nitrogen per Kg. of body weight per day has to be given. Plasma administration may be the only effective way to restore normal plasma protein levels rapidly until the general protein deficit has been corrected.

COMMENT

It has been shown that for various reasons evaluation of the protein nutritional status of a patient is exceedingly difficult and that the reliance placed on clinical methods is justified only to some extent in uncomplicated malnutrition. In many types of protein depletion measurements of the concentrations of total plasma protein, albumin and globulin give information which is not only incomplete but may actually be misleading, since the results may indicate success of protein therapy when in reality the state of depletion is not materially altered by the measures employed.

There are ways to improve the value of these methods and to approach the problem in a more rational fashion. Estimation of plasma volume simultaneously with protein concentration is an improvement and the technics[20,21] are relatively simple provided conditions are well controlled. A Kjeldahl method for nitrogen determinations, even though cumbersome, should be used whenever possible for the determination of plasma protein. Nitrogen balance and water balance studies, of course, provide the most complete information. Obviously, such investigations cannot be carried out in daily practice.

For adequate evaluation of the protein nutritional status and of the patient's progress under protein therapy the following procedures are suggested: (1) daily weighing under similar conditions; (2) records of fluid intake and output; (3) records of total nitrogen intake; (4) determination of hematocrit and (5) plasma protein concentration determination by a Kjeldahl method.

Daily weighing is possible in most patients with the present methods of early ambulation and relatively simple procedures enable one accurately to weigh patients in bed. In many types of malnutrition the weight alone will serve as an excellent guide for the evaluation of therapy provided there is no edema.

Knowledge of the patient's *fluid balance* gives an excellent measure of his state of hydration and once this has become stabilized a fair estimate of the plasma volume can be made on the basis of body weight accepting the assumption that the plasma volume is 5 per cent of body weight.[22] These considerations hold only in the absence of ascites or edema. Even in the presence of edema, however, the simple procedures of weighing the patient and following his fluid intake and output will provide valuable information on the state of nutrition and hydration.

A *record of the total nitrogen intake* is particularly helpful in the postoperative phase and should be kept whenever protein therapy is being administered. It is surprising how low in protein are some of the regimens used routinely in many institutions for postoperative nutrition. The simple order left by the physician that a high protein diet be given is not sufficient as

the actual intake is often far below the desired levels.

The simple procedure of *determining the hematocrit value* in a Wintrobe tube can provide information on many factors such as sedimentation rate, hemoglobin concentration and red cell volume, icterus index and plasma volume. This is a most valuable adjunct for evaluation of the protein nutritional status and is not used often enough.

In the light of the data available from the above procedures the figures obtained for *protein concentration of blood plasma* gain an altogether different significance than when they are used alone and a fair estimate of the patient's protein nutritional status becomes possible.

As to the determination of albumin and globulin concentration it is our impression that this best be omitted unless electrophoretic or immunologic methods are available. For purposes of following the response of a patient to nutritional therapy the determination of albumin by the Howe method may be more misleading than helpful.

Using the methods described for the evaluation of the protein nutritional status of patients, one will find various types of hypoproteinemia as described earlier: (1) hypoproteinemia without general tissue depletion that will be readily and permanently correctible by plasma infusions, or by blood transfusions if complicated by anemia; (2) hypoproteinemia with general tissue depletion which will respond to massive and prolonged oral protein therapy unless there are factors interfering with protein absorption or digestion (malnutrition, chronic loss from wounds, gastrointestinal lesions other than cancer, etc.); in the postoperative phase, types 1 and 2 are often combined; (3) hypoproteinemia that will persist in spite of tissue protein repletion, such as in gastric cancer, tuberculosis, certain types of renal disease, idiopathic hypo- and dysproteinemias. In these instances both high oral protein intake and administration of plasma by vein will be necessary. (4) Finally, hypoproteinemia obscured by hemoconcentration but the other criteria will show that there is tissue depletion and restoration of normal hydration will reveal the true degree of hypoproteinemia.

SUMMARY

Pitfalls and shortcomings of some of the methods used to evaluate the protein nutritional state are discussed. Some peculiar situations have been described in which evaluation of protein nutrition is particularly complicated and in which the response to protein therapy is unusual.

Methods for better evaluation of the protein nutritional state are suggested, permitting the classification of various types of hypoproteinemia into groups requiring different types of protein therapy.

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Clinic on Psychosomatic Problems

A Case of Hysteria

THE clinics are designed to bring out psychosomatic relationships both in symptomatology of the patient and in the organization of the hospital. Reports are directed by Drs. Stanley Cobb and Allan M. Butler and are edited by Dr. Henry H. W. Miles. This is a report of a staff meeting of the Psychiatric Service of the Massachusetts General Hospital. The preparation of these psychosomatic case histories receives support from the Josiah Macy, Jr. Foundation.

DR. RICHMOND HOLDER: The patient (M. G. H. No. 292026), a twenty-five year old married woman, entered the hospital complaining of numbness and weakness of the left leg of six months' duration, together with pains in the left groin and rectum. She dated the onset of her illness to a hemorrhoidectomy thirteen months before. While recovering from this operation, she had several "convulsions" manifested by twitching of the face, choking respirations and uncontrolled writhing in bed. She herself could remember nothing of these spells.

Rectal complaints persisted despite dilatations and a second operation was performed. Following the latter, sharp pains occurred in the left groin which soon radiated down the left leg. The patient lost her appetite and gradually her weight declined. Nine months before admission she had a severe spell of weeping and trembling.

Six months prior to admission the pain became constant and generalized over the entire left lower extremity. The patient was treated by several physicians and finally had a spinal manipulation under pentothal anesthesia. From that day on there was complete numbness of the leg.

The patient was admitted to another hospital for diagnostic work-up; lumbar puncture and pantopaque myelogram revealed no abnormalities. A presumptive diagnosis of hysteria was made and she was referred to the Massachusetts General Hospital for psychotherapy.

The past medical history included tonsillectomy at the age of four years and the usual childhood diseases. There were no early neurotic traits except nail biting. Five years before the present illness there had been an acute episode of abdominal pain, nausea and vomiting. Exploratory laparotomy revealed a normal appendix. An aberrant renal artery was found and ligated but this was not believed responsible for the symptoms.

The patient was the only child of an unknown father and a delinquent mother. She was adopted when she was four years old by a strict, middle-aged, childless Scotch couple and was never told anything about her real parents. She recalled being teased about this by her playmates, and also remembered that when she was unruly her foster parents would reproach her with the fact that she was adopted. Her foster mother was a cold, exacting woman whom the patient resented, but she was very fond of her foster father and could confide in him.

She finished high school without difficulty and apparently made an adequate social adjustment. In her sophomore year at college she had a "nervous breakdown" and had to quit. At first the details of this illness were not obtained as the patient could not remember what had happened. Later it came to light that she had been unhappy at college because her foster mother interfered with her personal affairs and gave her an inadequate allowance although the family was well off financially. One day the patient was found lying unconscious on the floor of her room and after a brief period of hospitalization she was sent home. No organic cause for the episode was found.

She then began nurses' training but quit to be married after a brief courtship at the age of twenty-one. She was always frigid though she did not find intercourse unpleasant. There were two uncomplicated

pregnancies and both children were healthy. The patient's husband, since discharge from the Army, had found himself stuck in an unsatisfactory job and had been drinking quite heavily.

Upon physical examination the pronounced limp was noteworthy. Dragging her left foot, the patient walked with a wide base and yet was able to support her entire weight upon the left leg. This extremity was cooler than the right and slightly cyanotic. The deep reflexes were bilaterally equal and brisk. There was anesthesia of the left lower extremity and loss of vibratory and position sense from the inguinal ligament down. Voluntary muscle strength of the left leg was diminished but there was no atrophy. The remainder of the physical examination revealed no further abnormalities.

Laboratory data, including urinalysis, complete blood count, Hinton test, chest x-ray and basal metabolic rate were normal. The electroencephalogram was considered a borderline record by reason of occasional slow waves, but there was no evidence of a dysrhythmic focus.

Psychotherapeutic interviews were then begun. The patient at first related her attitude toward her mother-in-law who resented the patient's higher social status and made remarks about her parents being stingy. A good deal of hostility was evident and she was encouraged to speak of it freely. (One usually finds that negative feelings are more easily expressed toward a person with whom the patient does not have a strong emotional tie.) She then told that she had married to get away from the strictness of the foster home. While her husband was in the Army, she had lived with his mother and sister-in-law. Her younger baby was a few months old at the time, adding to her burden, and the household was in a continual state of tension and unexpressed ill-will. (It is interesting that her rectal pain became worse at this time and the first operation was done.)

Because her relationship with her adopted parents seemed important in various incidents, the interviews were then directed toward that general topic. Soon it was noted that she talked mostly about her stepfather, and so the focus was narrowed to her feelings and attitudes toward him. She told how he always took her part in family quarrels which made her feel better. Then one day, with tremendous emotional feeling and tears, she poured out a flood of information. Shortly before her first operation the father was found to have a carcinoma of the prostate. During the next few months he rapidly became worse. His legs were weak, he walked with difficulty, and the last time she had seen him before her back manipulation he had been walking with a cane. (From that time on she herself could not walk without a cane.) The psychiatrist at this point kept his own activity to a minimum, merely encouraging the patient to talk and gently directing her toward the topics which seemed most emotionally charged. No interpretations were made.

In the next interview she again wept as she told of her shock at the realization of her father's impending death. For a long time she could not admit it to herself. She said: "I can remember saying to myself, 'Why couldn't it be me? I've disappointed him . . . made a poor marriage and got into a terrible family. If I lose my father, I've lost that good part of my life . . . the others don't mean anything to me.' Last night I realized his symptoms were so like mine and I wanted to take them on myself. I feel terribly guilty. I want to make myself suffer. It's too late to make it up to him now. I never cried about it before. I always put it out of my mind."

At the end of this interview she threw down her cane, saying: "I don't need this to walk with any more," and limped out of the room unaided. On the following day sensory examination of the leg was normal and the lividity had disappeared.

When presented at the Staff Conference, the patient walked into the room easily with only a trace of a limp. She was cheerful and pleased with her improvement and stated that her leg was almost as good as ever.

DISCUSSION

DR. STANLEY COBB: This is more satisfactory than if we had used amytal narcosynthesis and I believe more permanent than if we had gone right ahead and used suggestion. We have rid her of the symptom by insight therapy and that is excellent. We will have on our hands a woman who had a monosymptomatic hysteria, who is in difficulties with her husband, and in a social situation that does not sound easy to help. From now on shall we use more psychotherapy of this sort? It is obvious that she needs more social service in trying to arrange her life. She should get out of those five rooms; she will soon be upset by the loss of her father.

DR. HOLDER: Her foster father will live from three to nine months. When he dies the financial situation will improve because he has set up a trust fund. The husband now has a steady job and uses less alcohol.

DR. JACOB FINESINGER: I do not think she is cured yet. We do not know specifically the particular problem she had. Unless you lead onto this problem you do not get far. She identifies with her father. I do not think Dr. Holder suggested that to her. It is rare to have a patient explain her experiences as clearly as this. I should like to spend several hours going over the material. The question of *why* it happened I should leave out; *how* it happened could be interpreted to her. Emphasizing her social adjustment, I would have her become active again and use her leg as much as possible. I would see her once a week. This case illustrates the limitation of this kind of therapy. One can get results like this without going back into childhood material. However, in analysis we would not be satisfied. We would want to know why she had guilt and why she identified. We would attempt to learn about her earlier experiences.

DR. BERNARD BANDLER: Dr. Holder should continue to see her because her father is dying. After his death one can anticipate some reaction. I was interested in the way this came out because the intellectual insight was the last stage. That brought up tremendous effect. The next day she put together the puzzle. The effective thing was her ability to react with emotion while going over this material.

DR. COBB: In order to make a prognosis we must have an accurate and full past history. We must know the number of episodes, the kind of symptoms and how long she has had them. We must evaluate the severity of the emotional crisis which was the immediate precipitant of her present attack. If there is a long past history of numerous episodes with mild precipitants, one is less happy than with a girl like this whose history is not too disturbing.

SUMMARY

A positive diagnosis of hysteria should be made from the clinical picture and from a study of the patient's reactions to life situations. Hysteria occurs mostly in women and typically consists of three components: childishness, conversion symptoms and amnesia. The patient gets into an intolerable situation (conflict) from which she "escapes" by the development of symptoms. She has no memory of the thought processes that have led to such an escape. (The conflict is repressed.) Patients with hysteria often blandly accept their symptoms, and this striking lack of concern has been called "belle indifference."

The symptoms mimic neurologic and medical disorders and include pain, paralysis, sensory disturbances, peculiar gaits, loss of vision, hearing or smell, stiff contracted limbs, vomiting, syncope, fits, hyperventilation and frigidity.

The medical history in this case offered a number of clues. The curious "convulsions" with amnesia strongly suggested hysteria although epilepsy had to be considered and ruled out. Actually there was little resemblance to epileptic seizures, and the electroencephalogram showed no epileptic discharges. The acute attack of abdominal pain with removal of a normal appendix and the episode of unconsciousness and amnesia at college were both

typically hysterical. Finally an unequivocal diagnosis could be made upon the physical findings which were incompatible with a neurologic lesion. As the illness was investigated further and the correlation between symptoms and situations unfolded, the meaning of the conversion symptoms became clear.

In the differential diagnosis of weakness, pain and anesthesia of a single extremity, many possibilities exist. The pathologic process may be inflammatory, toxic, degenerative, traumatic or neoplastic. The lesion may be located (1) in peripheral nerve, (2) in the lumbosacral plexus, (3) in the spinal roots or (4) in the central nervous system. Depending upon the structures affected, various neurologic signs will result.

The important point in this case was that the deep reflexes were normal in the paretic leg. They were brisk and equal to those in the right leg. Babinski's sign was absent. The anesthesia was of the "stocking" type, involving the entire limb from the inguinal ligament down. The muscles of the extremity were weak but there was no atrophy, and the weakness involved the limb as a whole rather than specific muscles or muscle groups. There was neither spasticity nor a true flaccid paralysis. There had never been any disturbance of sphincter control.

A lesion involving peripheral nerve pathways would cause a diminution or loss of deep reflexes, and the sensory loss would correspond to the cutaneous distribution of peripheral nerves or to the appropriate dermatomes. Muscular weakness would involve specific muscles or groups of muscles and the paralysis would be of the flaccid type. In a process of six months' duration one would expect some degree of muscle atrophy.

In a lesion in the tracts of the spinal cord or in the brain deep reflexes would be hyperactive and paralysis would usually be spastic, with Babinski's sign. Ordinarily there would be no sensory loss; but if present, there would be sensory dissociation, i.e., selective anesthesia according to the tracts involved.

An important differential sign was elicited as follows: With the patient supine, the examiner placed his hands, palms up, under her heels. She was ordered to sit up whereupon both heels pressed down upon the examiner's hands. If the weakness had been due to a neurologic lesion, the *affected leg would not have pressed down* and might even have risen off the table as the patient sat up. (This is known as "Babinski's second sign.")

Characteristically, the paresis in hysteria involves a functional unit as a whole: a hand, an extremity or half the body (with a sharp midline demarcation.) "Glove" or "stocking" anesthesia is typical. The area and degree of anesthesia may vary with repeated examinations or by suggestion on the part of the physician.

In the management of hysteria it is important to avoid frequent examinations and laboratory procedures once the diagnosis has been made. Patients are prone to develop new symptoms and the physician may be tempted to embark upon a further course of diagnostic studies. Examinations and tests should be completed within a few days and psychotherapy instituted as soon as possible.

In the therapeutic interviews a definite plan was followed. First, the emphasis was not upon accumulating a large amount of diffuse material pertaining to all aspects of the patient's life, but rather upon the emotionally significant situations which precipitated the major symptoms. (It would have been interesting to find out more about the episode at college and the appendectomy, but these topics were not in line with the immediate goal and therefore were not discussed in detail.) Second, efforts were made to "focus" the material toward selected limited goals in order to bring out the relationship between situations and symptoms.

The psychiatrist directed the interview with as little activity on his part as possible, encouraging the patient to talk by a show of interest or if necessary by mild commands

such as, "Tell me more about this." Direct questions or leading questions were avoided. No disturbing interpretations were made; although after the patient had seen the relationship between her adopted father's symptoms and her own, the therapist reviewed the material thoroughly with her.

In the staff meeting the limitation of this type of brief psychotherapy was pointed out and prognostic guides were discussed. Further psychotherapy with social service aid was planned. In general the therapeutic process in hysteria is not as dramatic as in this case but is a long term job involving the combined efforts of the psychiatrist and the social worker. Actually it amounts to an emotional "re-education" process whereby the patient learns new methods of handling life situations, i.e., "grows up."

After discharge from the hospital the patient was seen for a month in the Out-Patient Department and continued to be symptom-free. Her therapist left the hospital staff and she decided that she would prefer not to see another doctor as she felt quite well. She has not returned in nearly two years but reports by telephone that she is still doing well.

Clinico-pathologic Conference

Obesity, Hypertension, Diabetes and Heart Failure*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, F. G., (B. H. No. 148217), was a fifty-eight year old white married housewife who entered the Barnes Hospital on June 17, 1947, complaining of pain in her chest and back and of obesity.

The patient's father had died of heart disease at the age of fifty-five but otherwise the family history was non-contributory. The patient herself, had had no significant illness in her youth and at the age of twenty she weighed 130 pounds. In the fifteen years following her marriage she gave birth to six normal children, but during this period she gained approximately 200 pounds and carehed a maximum weight of 325 pounds which was maintained for about ten years until one year before her death. For ten years prior to admission she had noticed increased hair on her arms, legs and face, and five years before entry she had an episode of vaginal bleeding which lasted several weeks. Dilatation and curettage were performed at an outside hospital and the patient was told that she had no cancer. Subsequent to the operation, however, she received radium treatment. Four years before entry she developed polyuria and polydipsia. She consulted a physician who told her that she had sugar in her urine and she was advised to take 30 units of regular insulin every morning. She followed this regimen for an indefinite period but had taken no insulin for months prior to admission to this hospital. For a period of approximately ten years she had had moderate dyspnea on exertion and also some palpitation; on several occasions her physician advised her to avoid overexertion because of her heart. Upon a number of examinations she was told that she had high blood pressure but she did not know the levels attained. During the year before entry, although her appetite continued to be voracious, she lost 105 pounds.

Approximately two months prior to entry the patient awakened one morning with a knife-like pain in the left chest which radiated rather diffusely around to the left shoulder and back. The pain was so severe that for two nights she was unable to lie down. She was seen by her physician who prescribed medication which brought some relief, and gradually over the course of a week the pain decreased to the point where the patient was able to resume light household duties. Shortly thereafter, however, pain returned with increased intensity and was noted in both sides of the chest anteriorly and in the back at the level of the scapulae. It was described as being made worse by motion and by deep breathing and eventually became so severe that the patient was almost totally incapacitated. During the month before entry she spent most of each day in a chair. Two weeks before admission she noticed swelling of the ankles which became worse in the evening. Because of these complaints she sought admission to the Barnes Hospital.

At the time of entry physical examination revealed the temperature to be 37.8°C.,

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pulse 84, respirations 18 and blood pressure 220/130. The patient was an extremely obese white female who lay on her left side and screamed with pain when any attempt was made to move her. She was slightly dyspneic but not cyanotic. The fat distribution was chiefly confined to the breasts which were huge and pendulous and to the abdomen where an enormous panniculus extended in front of her. The arms, legs and especially the thighs showed evidence of great weight loss but were comparatively well proportioned. Intertrigo was present in the body folds. The hair on the scalp was sparse and dry but there was a coarse mustache on the upper lip and a moderate amount of black hair on the arms and legs. Examination of the eyes revealed that the pupils were round, regular and equal and reacted well to light and accommodation. The fundi showed normal discs and slightly tortuous vessels. No abnormal findings were noted in the nose, mouth or throat. Examination of the neck was likewise not remarkable; the thyroid was not palpable. Because of the patient's immobility, examination of the lungs and heart was difficult, but there was dullness over the base of the right lung posteriorly and in that area tactile fremitus was decreased and breath sounds diminished. Above this area a few râles were heard. The heart border could not be percussed and the sounds were distant. The rhythm was regular. There was a grade II systolic murmur at the apex and the second aortic sound was accentuated. Because of its huge size, the abdomen could not be palpated properly. Pelvic examination revealed a healed cervical scar and a lax perineum but no other findings could be made out. The clitoris was not enlarged. Rectal examination was negative. There was no lymphadenopathy and the neurologic examination seemed within normal limits. Two plus edema of the ankles was present and there were distended veins over the sixth and seventh dorsal vertebrae.

Laboratory findings on entry were as follows: Blood count: red cells, 4,890,000; hemoglobin, 12.5 Gm.; white cells, 7,950; differential count: eosinophiles, 1 per cent; juvenile forms, 3 per cent; stab forms, 13 per cent; segmented forms, 53 per cent; lymphocytes, 26 per cent; monocytes, 4 per cent. Urinalysis: sugar, trace; albumin, negative; sediment, negative. Stool examination: guaiac negative. Blood Kahn test: negative. Blood chemistry: fasting blood sugar, 237 mg. per cent; non-protein nitrogen, 21 mg. per cent; total protein, 6.0 Gm. per cent; albumin, 3.4 Gm. per cent; globulin, 2.6 Gm. per cent; calcium, 11.3 mg. per cent; phosphorus, 5.2 mg. per cent. Venous pressure: 220 mm. of saline. Circulation time (decholin): 15 seconds. Basal metabolic rate: plus 45; plus 49. Roentgenograms: "X-ray of the chest reveals the cardiac shadow to be enlarged 3°. The aorta is tortuous and contains a plaque of calcium in its arch. The trachea appears shifted to the left but the film is not well centered. There is questionable compression of the anterior portion of the body of the 12th dorsal vertebra. There also appears to be a large destructive area in the manubrium sterni. A lateral view of the skull reveals hyperostosis frontalis interna." Electrocardiogram: right axis deviation; occasional ventricular premature contraction.

Shortly after her admission to the hospital the patient was noted to be perspiring profusely and upon close questioning it was learned that similar episodes had occurred frequently for many years. Cyanosis appeared and in view of the other signs of cardiac insufficiency, including dyspnea, cardiac enlargement, increased venous pressure and hydrothorax, the patient was digitalized. She was placed on a controlled diet without insulin although subsequently insulin was given. Further laboratory studies revealed the blood chlorides to be 83 mEq./L., blood sodium 144 mEq./L. and the carbon dioxide combining power 45.2 volumes per cent. A glucose tolerance test was performed and the blood sugar was found to be 321 mg. per cent at four hours and 261 mg. per cent at five hours. A concentration diuresis test showed the specific gravity to range from 1.021 to 1.028. A

phenolsulfonphthalein test was performed and 45 per cent of the dye was excreted in two hours.

A gynecologic consultant was asked to see the patient but because of her weight and inability to cooperate his examination was unsatisfactory.

The patient was seen by an orthopedic consultant who thought that the back pain was due to senile osteoporosis with a compression fracture although it was thought that a metastatic lesion could not be ruled out. A fracture board was placed under the patient's mattress and she was given infrared treatments with some relief. Aspirin was prescribed in an effort to ease her pain. The patient continued to insist upon lying on her left side. About ten days after admission some of the signs of cardiac insufficiency improved although râles still persisted in her chest. During this period a low grade fever was recorded which was not affected by 30,000 units of penicillin every three hours. About two weeks after admission the patient became rather disoriented, increasingly uncooperative and a very difficult nursing problem. As was stated insulin had been instituted in order to achieve better control of the diabetes and during the third week her fasting blood sugar was 184 mg. per cent. Other laboratory findings included a non-protein nitrogen of 136 mg. per cent, chlorides of 82 mEq./L. and carbon dioxide combining power of 58.2 volumes per cent. Repeated urine examinations showed 3 plus sugar and 3 plus albumin; occasional granular casts appeared in the sediment. Further electrocardiograms showed no change from that on admission except for the appearance of digitalis effect. On the twentieth hospital day the patient became obtunded and during the next several hours her blood pressure rapidly fell to a level of 120/68 and her pulse rose to 110. Her temperature at that time was 38.2°C. Her respirations became rapid and labored. Physical examination failed to reveal evidence of thrombophlebitis in the legs or signs of pneumonia in the chest. However, the patient became progressively worse and she expired quietly on July 8, 1947.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Before we begin our discussion of this extremely complex case I should like to ask Dr. Bottom if he has any further comments on the x-ray films.

DR. DONALD S. BOTTOM: As was stated in the protocol the films were rather poor, first because of the patient's obesity and second because of her inability to cooperate. The chest film showed marked cardiac enlargement, prominence of the aorta and fluid at the left base. Not only were there marked hypertrophic changes in all of the dorsal vertebrae but also compression of the anterior portion of the body of the twelfth vertebra. No areas of bone destruction were present in the skull.

DR. ALEXANDER: This patient was afflicted in a great many ways: obesity, diabetes, hypertension, arteriosclerosis, cardiac failure, a high metabolic rate and hirsutism all may be listed among her abnormalities. How many of these we may incorporate into our final diagnosis or diagnoses remains to be determined. It seems to me that the most obvious problems were her obesity and diabetes. The endocrinologic aspects of a case such as this are extremely involved and our time is limited. I should like to begin, however, by asking Dr. MacBryde if a single endocrine gland was incriminated primarily in this case.

DR. CYRIL M. MACBRYDE: Taking into consideration the group of symptoms and signs presented by this patient, one would immediately think of the pituitary gland, and I would think it quite likely that there was a disturbance in the anterior pituitary, particularly in the basophil cells. However, I would at once like to qualify my statement by saying that such changes may be associated with other glandular defects and may not be the cause of obesity *per se*. It is known that actual histologic changes in the pituitary are not demonstrable as a rule in any of the usual obesity syndromes and

when one damages the pituitary experimentally no specific type of obesity can be produced. On the other hand, if either the hypothalamus or the supra-optic nuclei are damaged, with or without pituitary injury, obesity often results.

DR. ALEXANDER: You mention the basophilic cells. Do you believe that when the pathologists present sections of the pituitary there will be an organic change in this gland or do you believe that the clinical changes were functional instead?

DR. MACBRYDE: It is most difficult to answer your question. I have seen patients with syndromes clinically similar to those under discussion here in which no pituitary changes were found. On a percentage basis, however, it would seem likely to me that either a basophilic adenoma or hyalinization of the Crooke cells in the anterior pituitary would be present. Indeed, both may be found.

DR. ALEXANDER: Dr. Williams, do you concur in this opinion?

DR. RAY D. WILLIAMS: Yes, I should say there was about a fifty-fifty chance of finding a structural lesion in the pituitary.

DR. ALEXANDER: Do you believe any other structures will be involved in this case?

DR. MACBRYDE: Certainly the adrenal cortex will show abnormalities.

DR. ALEXANDER: Do you think the adrenal changes are due to an adrenotropic hormone?

DR. MACBRYDE: The relationship is obscure. Apparently a connection exists between the pituitary changes and those which occur in the adrenal. In this case there may be diffuse hyperplasia of the cortical cells in either one or both adrenals. It is also likely that one or more adenomas will be present; indeed, in this patient there is the suggestion that there may be a carcinoma. The x-ray findings are consistent with metastatic lesions. You will recall that there was a defect in the sternum and collapse of one of the dorsal vertebrae. Collapse of vertebrae is common in pituitary basophilism on the basis of extreme osteoporosis, but I am particularly interested in the sternal lesion and would attribute that more likely to carcinoma; that is, to malignant changes occurring in an adenoma with resultant metastases.

DR. ALEXANDER: You are quite sure then that there will be either hyperplasia and/or adenomas of the adrenal cortex and you further believe that these changes are certainly more apt to be found than pituitary abnormalities.

DR. W. BARRY WOOD, JR.: If there is adrenal cortical adenoma, will there also be Crooke's changes in the pituitary?

DR. MACBRYDE: Yes, the adrenal abnormality is apt to be a tumor in Cushing's syndrome. No basophil adenoma may be found but the Crooke's hyalinization of the basophil cells is practically always present.

DR. ALEXANDER: Dr. Wade, would you comment on the symptoms which may arise as a result of hyperactivity of the adrenal cortex?

DR. LEO J. WADE: Several groups of hormones can be attributed to the adrenal cortex. I think that Fuller Albright's analysis is a good one. As you will recall he attributes some of the symptoms to an "S" or sugar hormone which presumably produces diabetes by interfering with the normal utilization of amino acids; this abnormality is also responsible for osteoporosis because it prevents formation of an adequate bone matrix. It probably has something to do with obesity also for by interfering with amino acid and protein metabolism, fat is produced in abnormal quantities. The masculinizing signs are attributed to an androgenic hormone or hormones—Albright's "N" hormone. Finally there are substances which have to do with salt and water metabolism. Hypertension, which is a common manifestation in this group of patients, is in my opinion difficult to correlate with any of the particular principles.

DR. HENRY A. SCHROEDER: It seems fairly well proven that hypertension depends upon some change in the adrenal cortex because when tumor is present its removal

may lead to disappearance of hypertension. The influence of the salt-retaining hormone on hypertension has been a subject of much speculation recently. There seems to be evidence, in at least some patients with hypertension, that there is some disturbance in salt metabolism. The synthetic salt-retaining hormone, desoxycorticosterone acetate, when given intramuscularly along with salt has been shown to elevate blood pressure in both normal individuals and in hypertensives. Normal patients, however, are much more resistant to this change and it may take a great deal longer to produce any significant change in the blood pressure in normals whereas in hypertensives the change may be seen in a few days or even in one day. In hypertensives intravenous injections of DCA have been found to lead to further elevation of blood pressure.

DR. ALEXANDER: Returning to the obesity, the fat distribution in this woman was apparently not uniform. The lower extremities were described as being fairly well proportioned and most of the adipose tissue was confined to the trunk. Are these facts of significance?

DR. WILLIAMS: The tendency with pituitary basophilism or Cushing's disease is for the fat to become distributed chiefly on the trunk rather than on the extremities. As I recall no mention was made in the protocol as to whether the patient had a "moon" face.

DR. WADE: There is one other possibility that should be mentioned in regard to involvement of the endocrine glands. The change in the sternum might have had something to do with a lesion of the thymus gland. I have never seen such a patient but there are reports in which a tumor or hyperplasia of the thymus gland has supposedly been responsible for changes such as are recorded here instead of a primary lesion of the pituitary or of the adrenal.

DR. ALEXANDER: Do you have any comment, Dr. Bottom?

DR. BOTTOM: There was some discussion in the x-ray department as to whether the sternal lesion could have been an anomaly. In the lateral view there is certainly no evidence of a mediastinal mass that would suggest a tumor or hyperplasia of the thymus gland.

DR. CARL V. MOORE: I should like to hear further comment on the increased menstrual bleeding. Is it of significance and may it be correlated with the diagnosis of Cushing's syndrome?

DR. MACBRYDE: The patient was fifty-eight years old when she died and the abnormal bleeding occurred five years before entry. We do not know whether she had been amenorrheic prior to this episode of vaginal bleeding or whether she had been menstruating up until that time.

DR. HENRY H. GRAHAM: As far as we could determine there had been no menstrual irregularity previously.

DR. MACBRYDE: Usually when pituitary basophilism or adrenal adenoma is associated with the adrenogenital syndrome and masculinization there is amenorrhea. Patients may have either complete or intermittent amenorrhea but occasionally they do have periods of menorrhagia. In my experience when menorrhagia does occur it usually follows long periods of amenorrhea. Conceivably a similar situation applied here but because of the lack of information I am not able to make any further interpretation.

DR. ALEXANDER: This patient was obese for approximately thirty-five years. In Cushing's syndrome is not obesity usually of more rapid onset? Is it conceivable that this patient had Cushing's syndrome for thirty-five years?

DR. MACBRYDE: In Cushing's disease, with a basophil pituitary adenoma as distinguished from Cushing's syndrome, the course is a rapidly progressive one with sudden appearance of obesity and death of the patient within a few years. The symptoms here are more in keeping with Cushing's syndrome due to adrenal hyperplasia or adenoma.

DR. LLEWELLYN SALE, SR.: What about the possibility of an ovarian lesion?

DR. WADE: I believe that is a good sug-

gestion. The patient might have had either an arrhenoblastoma or a granulosa cell tumor, both of which are known to be masculinizing. When one sees a patient such as this, one of those two tumors should be kept in mind and a careful pelvic examination should be done in an attempt to identify or exclude them. When this patient had the dilatation and curettage, she was told that she had no cancer but she was apparently given radium; and one wonders why that therapy was instituted. She had been hirsute for ten years, however, and I would be skeptical that either an arrhenoblastoma or a granulosa cell tumor would be compatible with survival for that long a period. Either tumor would also leave unexplained the obesity which existed for such a long period of time.

DR. ALEXANDER: Is it conceivable that the patient had an adenoma for some years which subsequently became malignant? In that way perhaps one would explain the long period of hirsutism prior to the terminal illness.

DR. MACBRYDE: I believe that originally benign cortical adrenal adenomas may become carcinomatous.

DR. MARGARET G. SMITH: Some of the large adenomas associated with Cushing's disease have been questionably malignant.

DR. ALEXANDER: This patient had metabolic rates of plus 45 and plus 49, and the curves appeared to be satisfactory. What is your interpretation of these results, Dr. Wade?

DR. WADE: It is difficult to get an accurate measure of the metabolic rate of the patient when one relies upon the determination of the surface area to complete the calculation. The data are certainly unreliable in a patient of this size and therefore I am unable to attach any definite meaning to the basal metabolism recorded.

DR. MACBRYDE: I agree with Dr. Wade's comments, but hypertrophy of the thyroid has been found with changes typical of thyrotoxicosis in Cushing's syndrome.

DR. ALEXANDER: Do you think perhaps that there may be some hypertrophy of the thyroid gland?

DR. WADE: The patient has a rather low cholesterol which would be in keeping with the diagnosis of thyrotoxicosis but I am not able to substantiate it with any other findings.

DR. ALEXANDER: Now I should like to raise the question as to why this patient suddenly died. At the time of entry she was not cyanotic but subsequently she became so and she had many of the signs of cardiac insufficiency. Dr. Massie, do you believe that she died of a cardiac death because of a failing heart?

DR. EDWARD MASSIE: This is a situation in which the diagnosis of coronary occlusion may certainly find support. The patient was obese, diabetic and hypertensive. She had chest pain in the past and subsequently during her hospital stay her blood pressure fell to a low level and she died. This sequence is quite compatible with a diagnosis of myocardial infarction. Two points, however, stand out against that diagnosis: In the first place the patient had pain which was exquisite when she moved and she had pain when she took a deep breath. Such pain easily could have been due to the lesion in her spine rather than being of cardiac origin. In the second place the electrocardiogram, which of course is not infallible in making a diagnosis of myocardial infarction, does not show any of the changes which are attributable to coronary occlusion. Therefore, on the basis of these two factors I believe that the patient probably did not have a terminal myocardial infarction although I think she in all likelihood did have coronary artery disease.

DR. ALEXANDER: Do you believe that there will be a great deal of fat in the patient's heart?

DR. MASSIE: Yes, I am sure that fat deposition about the heart will be marked and I think there will be ventricular hypertrophy. Further, we should find signs of terminal cardiac failure.

DR. WOOD: I believe that we were suspicious of the possibility of pulmonary

embolism because of the patient's respiratory disturbance and chest pain. As a matter of fact, as I recall it, we considered that diagnosis as an explanation of her original attack.

DR. ALEXANDER: This patient was diabetic and obese. What would you predict as to the findings in her liver, Dr. Moore?

DR. C. V. MOORE: I would expect to find a moderate amount of fatty infiltration but otherwise I should think the liver would appear essentially normal.

DR. MASSIE: In view of the pain in the back and hypertension, dissecting aneurysm should be mentioned in passing as a possible cause of death.

DR. MACBRYDE: For the sake of completeness we should mention that this patient might have parathyroid adenomas which are rather common in this group of patienst.

DR. ALEXANDER: We have found today that patients with Cushing's syndrome may have thyroid enlargement, parathyroid adenomas, adrenal cortical abnormalities and pituitary changes. Do they have hypertrophy of the ovaries?

DR. MACBRYDE: At her age it may be difficult to be sure, but when these patients are subjected to surgical explorations, particularly those in the younger age group, atrophy and fibrosis of the ovary are frequently noted. One can say that this disease complex is really a syndrome of multiple endocrine abnormalities with the most striking findings in the adrenal.

DR. WADE: In view of the normal blood calcium and phosphorus do you believe that there is still a possibility of parathyroid adenomas to be considered?

DR. MACBRYDE: Yes I do because usually in these patients the blood calcium and phosphorus are normal.

DR. WILLIAM H. DAUGHADAY: I believe it is necessary to qualify the diagnosis of Cushing's syndrome here for some of the characteristic findings were absent. The patient apparently did not have a plethoric face, and she did not have purple striae which certainly would have been expected in view of the extreme obesity. Further, her skin was rather thick and somewhat oily in contrast to the usual description in Cushing's syndrome. It would have been helpful to have had determinations of the urinary ketosteroids and the urinary cortins; further, a glucose-insulin tolerance test might have demonstrated insulin resistance but the patient's condition did not permit these studies. The clinical features of this case resemble certain reports, which have appeared mainly in European literature, of "diabetes of the bearded woman" or the Aachard-Thiers syndrome which frequently have been associated with adrenal adenomas. Although adrenal adenomas occur commonly, hyperfunction is relatively rare. The fact that the patient had diabetes, hypertension and hirsutism does not establish the diagnosis of Cushing's syndrome. It has been shown that the incidence of adenoma in this type of case is higher than in the normal; likewise adenomas of the adrenal have also been shown to be associated with hypertension in a greater percentage of cases than in normals and finally, with increasing age itself there are more adenomas.

DR. ALEXANDER: You do not believe there will be a pituitary adenoma or pituitary changes?

DR. DAUGHADAY: I do not believe there will be changes in the pituitary but there may be an adrenal adenoma.

DR. WOOD: We were rather reluctant to make the diagnosis of Cushing's syndrome because we raised some of the same objections which Dr. Daughaday has offered.

DR. ALEXANDER: I believe we are all in agreement that this was indeed a complex problem. The general consensus appears to favor the diagnosis of adenoma of the adrenal cortex possibly with carcinoma and it is thought possible that there will likewise be basophilic changes in the pituitary.

Clinical Diagnosis: Cushing's syndrome; adenoma and/or carcinoma of the adrenal cortex; diabetes; hypertensive cardiovascular disease; cardiac insufficiency; arteriosclerotic coronary artery disease; osteoporosis; ?metastatic carcinoma of the sternum.

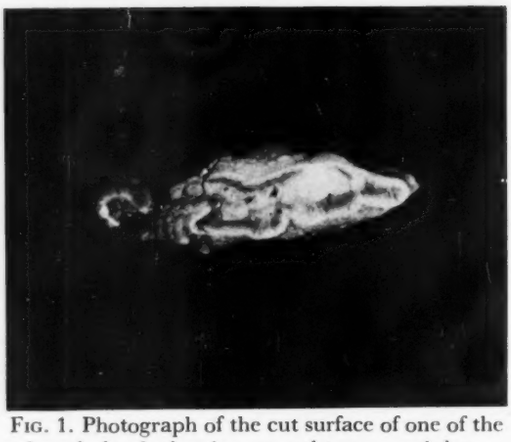

FIG. 1. Photograph of the cut surface of one of the adrenal glands showing several tumor nodules.

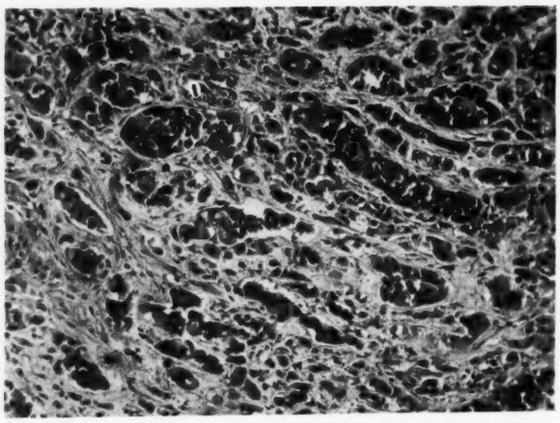

FIG. 2. Section of a lymph node showing an epithelial tumor.

PATHOLOGIC DISCUSSION

DR. JOYCE DAVIS: The body was that of a well developed, obese woman, 155 cm. in length and weighing 95 Kg. The breasts and the abdomen were large and pendulous and excoriation of the skin was evident in its many folds. Over the upper lip and chin there was a moderate growth of stiff black hair. Long black hair was present down the midline of the abdomen and on the legs. There was a broad diastasis of the abdominus recti muscles. As the pleural cavities were being examined the third, fourth and fifth ribs on both sides broke although no undue force was exerted. There were 200 cc. of yellowish, slightly turbid fluid in each of the pleural cavities but none in the peritoneal cavity. A few petechiae were present over the surfaces of the pleural cavities. The heart was hypertrophied and dilated, weighing 420 Gm. A few atheromatous plaques were present in the coronary arteries, but there was very little narrowing of their lumina. There was a patent foramen ovale of the guarded type and a few petechiae were seen over the pericardium.

The liver was large, peculiarly flat and weighed 1,940 Gm. Its outer surface was uniformly nodular as were the cut surfaces. The nodules varied in size from 2 to 3 mm. to 2 to 4 cm. in diameter and a considerable amount of yellowish fat was visible in them; firm, gray fibrous tissue separated them. Lymph nodes in the porta hepatis and in the thorax were enlarged, soft and bulged from the cut surface. The spleen was large, very soft and mushy and weighed 580 Gm.

The adrenal glands were quite unusual. The right weighed 11.4 Gm., the left 13 Gm. Both measured approximately 9 by 6 cm. Their external surfaces revealed no abnormalities. The cut surfaces, however, presented several fairly discreet, round yellowish-gray areas which differed markedly from the golden yellow color of the normal cortex. (Fig. 1.) After fixation other similar nodules were apparent. In the left adrenal there was also a grayish-white area in the medulla that was not as vascular and was much thicker than the medulla in the rest of the gland.[1]

DR. MARGARET G. SMITH: We shall have to rely upon the microscopic findings in order to arrive at a final diagnosis in this case. The large greyish-white lymph nodes were interpreted as containing tumor and we thus were faced with the problem of deciding where the primary tumor arose. No tumor was seen in the gross in any of the solid organs other than possibly in the adrenal glands where the nodules which Dr. Davis described were found. Beside a malignant tumor obesity, hirsutism, osteoporosis, cardiac enlargement and a clinical history of hypertension and diabetes were

[1] At the time of autopsy the sternum appeared grossly normal and only a routine section was made; through an oversight the pathologist was not apprised of the x-ray changes in the sternum and thus did not make a more detailed study.

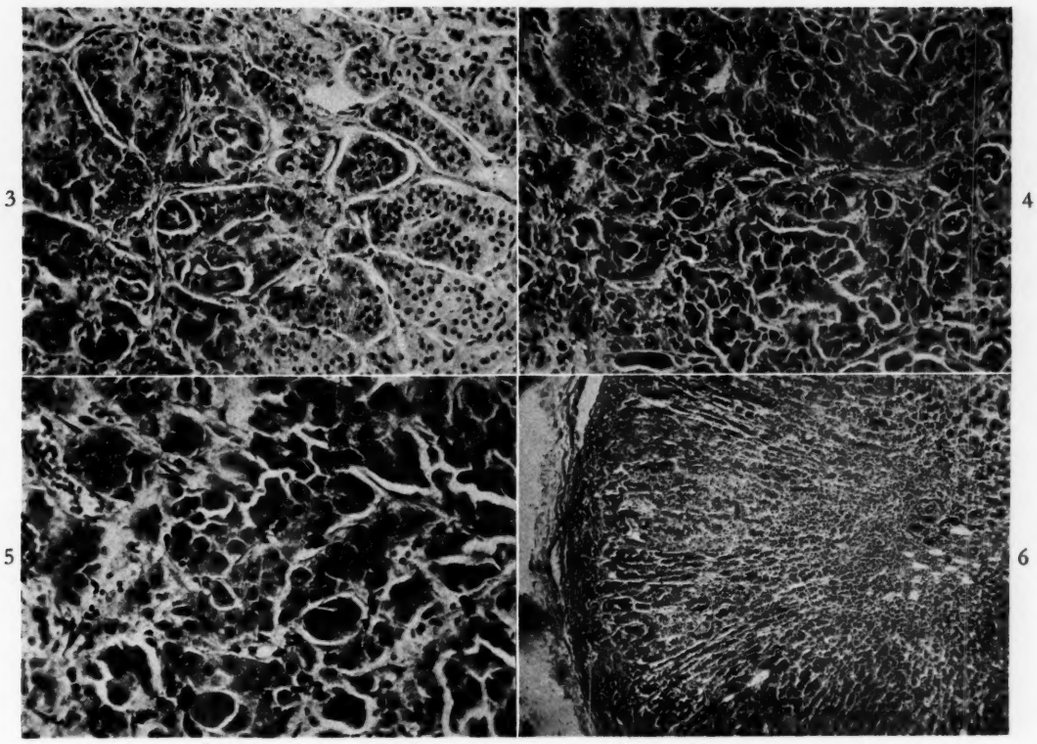

FIG. 3. A section of the adrenal gland through an area of focal hyperplasia.
FIG. 4. Another section of the adrenal through a nodule which shows definite malignant cells.
FIG. 5. High power view of the section seen in Figure 4. The character of malignant cells can be well seen here.
FIG. 6. An area of the adrenal cortex which does not show any focal hyperplasia. Note that the reticular zone appears quite wide.

present, all of which would be compatible with some major endocrine disturbance.

A section of one of the lymph nodes (Fig. 2) showed an epithelial tumor with considerable fibrous tissue proliferation. The tumor cells did not have a glandular arrangement; most of them had considerable cytoplasm, the nuclei varying from a vesicular type to a type with a smaller, deeply chromatic nucleus. From the appearance of the tumor in the node it was not possible to state where it arose, but it was certainly an undifferentiated epithelial tumor growing in sheets and cords. In another section of a lymph node there was necrosis in the center of some of the tumor nodules with calcification within the necrotic areas. The next section (Fig. 3) is from the adrenal and shows one of the multiple areas of focal hyperplasia. Similar changes were found in many other sections from the adrenal glands but these areas varied considerably in appearance. In some parts isolated cells closely resembled those from the cortex of the adrenal glands whereas in others the cells did not contain vacuoles and were deeply eosinophilic. In still other areas there apparently was further change in the cells so that they resembled the normal cortical cells even less. They had larger nuclei and more cytoplasm and were arranged in sheets. A section from another nodule (Fig. 4) shows definitely malignant cells. These cells are large and have deeply eosinophilic cytoplasm; their nuclei show considerable variation in size and chromatin content. The normal arrangement of cortical cells is lost. A higher power view of the preceding section (Fig. 5) shows the malignant character of the cells.

When one studied these sections of the adrenal, the tumor did not seem to have arisen in a single large nodule but rather from multiple adenomas or focal areas of

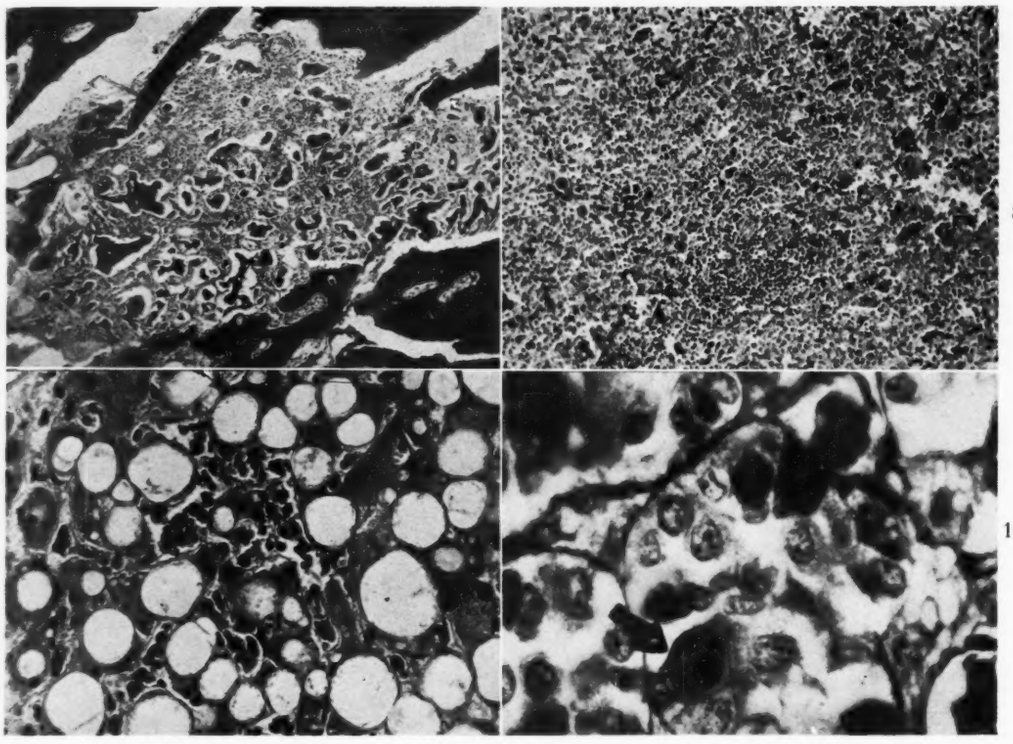

FIG. 7. Section from a vertebra showing infiltration of the tumor cells in a dense connective tissue.
FIG. 8. An area in the spleen where extramedullary hematopoiesis is quite prominent.
FIG. 9. Section of the liver showing fatty metamorphosis and hematopoiesis.
FIG. 10. Section of the pituitary in which the basophilic cells show Crooke's changes. Note particularly the cell indicated by the arrow.

hyperplasia. Because of our difficulty in deciding where the tumor arose, we were at first loath to consider it primary in the adrenal. It might have been metastatic to the adrenal, but there was no evidence of a malignant tumor elsewhere. Further, as we considered the relationship of the tumor to areas of focal hyperplasia the apparent transition in some areas was so striking that we concluded that this was indeed a carcinoma of the adrenal involving both glands. Probably the tumor rose in areas of hyperplasia in the cortex which in all likelihood were present for a long time.

Figure 6 is from an area of the cortex not showing the changes of focal hyperplasia. It is interesting that the reticular zone appears wide in this gland in comparison with the fascicular and glomerular zones. In some places one can see the pigmented cells of the reticular zones extending in strands up into the fascicular zone. The fascicular zone also seems to be hyperplastic throughout.

The next section (Fig. 7) is from a vertebra. There is a large amount of connective tissue and a small amount of new bone formation. Strands and sheets of tumor cells may be seen in the dense connective tissue. No hematopoiesis is seen in this section.

In the spleen (Fig. 8) there were numerous islands of extra medullary hematopoiesis of both erythrocytic and granulocytic cells. In the liver (Fig. 9) there was also a considerable amount of hematopoiesis and marked fatty metamorphosis.

The pituitary gland showed many eosinophiles but there was no adenoma. Some of the basophiles were normal in appearance; in Figure 10, however, there is seen a basophile (arrow) which shows degranularization and homogeneous cytoplasm containing vacuoles. With a differential stain

for cell granules, it was found that the non-granular cytoplasm of these cells was of the robin's egg blue color described by Crooke. This is the type of degranularization and hyalinization of the cytoplasm that one finds in Cushing's syndrome.

A section of the kidney showed some thickening of the basement membranes in the glomeruli but there was a surprisingly small amount of arteriolar change in view of the marked hypertension. In the pancreas there were many normal islands but some showed hyalinization.

In summary, we believe that the areas of focal hyperplasia in the adrenals probably had been present for some years and were related to the endocrine disturbance. More recently there were malignant changes in the areas of hyperplasia and subsequently metastases to the lymph nodes and bone marrow. As a result of destruction of the marrow, extramedullary hematopoiesis occurred. As far as the terminal episode is concerned the patient had fluid in her chest, an enlarged heart and other findings consistent with cardiac failure although there was not the marked degree of congestion in the liver and lungs that one usually finds under such circumstances.

DR. C. V. MOORE: It seems almost impossible that the blood count recorded on this chart is correct, and it is difficult to refrain from making some comment about it. The differential must have been incorrect. With so much extramedullary hematopoiesis and so much infiltration of the bone marrow, the patient must have had myelocytes or nucleated red blood cells or both in her peripheral blood. If those had been recognized, it would have pointed definitely to a myelophthisic process and the tumor might well have been diagnosed before death.

DR. ALEXANDER: Is this not a most unusual form of carcinoma?

DR. SMITH: Yes, it is. It is so unusual that to begin with I maintained that it was a metastatic tumor in the adrenal but I am now convinced that it was primary in the adrenal.

Final Anatomic Diagnoses: Focal hyperplasia of adrenal cortex; obesity (96 Kg.); hirsutism; osteoporosis; hyalinization of cytoplasm of basophil cells of pituitary gland; hyalinization of islands of Langerhans (history of diabetes); arteriolar nephrosclerosis, slight (history of hypertension); hypertrophy and dilatation of the heart (420 Gm.); carcinoma of adrenal cortex; metastatic carcinoma in porta hepatic, peripancreatic and tracheobronchial lymph nodes and in lymph nodes of the transverse mesocolon; metastatic carcinoma in the bone marrow, advanced, and in the liver; extramedullary hematopoiesis in the spleen and liver.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Lupus Erythematosus Disseminatus Sine Lupo with the Nephrotic Syndrome*

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THE criteria for the clinical diagnosis of lupus erythematosus disseminatus have been well formulated. The cardinal features are: (1) The erythematous lesion of the skin, frequently in butterfly distribution over the face; (2) constitutional symptoms of pyrexia, weakness, cachexia and loss of weight; (3) negative blood cultures; (4) arthralgia; (5) nephritides; (6) suppression of blood-forming elements, including leukopenia, secondary anemia and thrombocytopenia; (7) lymphadenopathy; (8) endocarditis (non-bacterial); (9) effusions into pericardial, pleural and less commonly, the peritoneal cavities; (10) predominant occurrence in females.

The above protean manifestations occur singly or in various combinations and are of varying duration. Until recently the skin lesion was thought essential for diagnosis but the analysis of Gross and Friedberg[1] in 1936 established the concept of disseminatus lupus erythematosus sine lupo.

This case is described because there are so few specific reports of the disease without the skin component.

CASE REPORT

E. C., a thirty-four year old unmarried white female of Italian parentage, was admitted to the Fourth Medical Division of Bellevue Hospital on April 18, 1946, complaining of intermittent swelling of the hands, legs and feet for the past two years.

Two years ago the patient developed intermittent attacks of painful and swollen fingers which were aggravated by cold weather. Asthenia, nocturia and polyuria became evident in the past year. In January, 1946 edema of the ankles developed, soon followed by swelling of the face, legs and hands which became progressively more severe and which persisted. Mild exertional dyspnea, without orthopnea, occurred at this time. Urinalysis revealed massive albuminuria. She was treated with a high protein diet but showed no improvement. In April, 1946 the patient developed frequent nausea and vomiting, accompanied by marked lethargy. One month before admission a detailed examination by her private physician revealed the following: Generalized edema; blood pressure, 144/88; marked albuminuria with a specific gravity of 1.008 to 1.014; severe secondary anemia; leukopenia; cholesterol, 267 mg. per cent; non-protein nitrogen, 74.2 mg. per cent; serum phosphorus, 6.4 mg. per cent and total protein, 4.1 Gm. per cent (albumin 2.9 Gm., globulin 1.2 Gm.). A diagnosis of chronic diffuse glomerulonephritis with marked impairment of renal function was made at this time.

Review of systems was non-contributory. The patient smoked two packages of cigarettes daily. She had typhoid fever as a child, frequent sore throats and colds until six years before admission and chronic bilateral otitis media since childhood with intermittent purulent discharge. There was no history of rheumatic fever, growing pains, joint pains or epistaxis. Her mother died at the age of thirty-nine from pneumonia and her father died at the age of seventy-two from arteriosclerosis. Three brothers and four sisters were all alive and well. There was no known history of kidney disease, tuberculosis, cancer, rheumatic fever or allergic disease.

Physical examination revealed the following: Temperature, 98.6°F.; pulse, 80; respirations, 20; blood pressure, 180/100. The patient was in no distress; she appeared to be her stated age

* From the service of the Fourth Medical Division, Bellevue Hospital, New York, N. Y.

and was well developed and fairly well nourished. There was 2 plus peri-orbital edema. The mucous membranes were pale and there were no hemorrhages. The head revealed no scars, deformities or mastoid tenderness. There was no gross disturbance of vision. The pupils were round, equal, regular and reacted to light and accommodation. Nystagmus was absent; external ocular movements were normal. Examination of the fundi was within normal limits. The right drum of the ear was perforated, with obliteration of land marks but no discharge. The left drum was scarred, thickened and retracted. No perforation was seen. There was impaired bilateral hearing. A small amount of encrusted mucus was present in the nose but there was no obstruction. The septum was intact. The tongue was pale but otherwise normal. Teeth were in poor repair and were carious. Tonsils were normal in size and there was no exudate or injection. There was no venous engorgement or abnormal pulsation in the neck. The anterior cervical glands were palpable bilaterally. The trachea was in the midline. The thyroid was not enlarged. The chest was symmetrical and expansion was equal. Breasts were of normal size and there were no scars or tenderness. No masses were palpable. The lungs were resonant and the breath sounds were vesicular. Tactile and vocal fremitus were normal; no râles were heard. The apex beat of the heart was in the fifth interspace at the mid-clavicular line. Cardiac dullness was within normal limits. No thrills were palpable. Sounds were of good quality; a blowing systolic murmur was heard at the apex transmitted to the pulmonic area. The pulmonic second sound was accentuated compared to the aortic second sound. There was regular sinus rhythm. The abdomen was slightly distended; it was soft and there was no tenderness. The liver, spleen and kidneys were not palpable. The genitalia were normal; rectal examination was normal. Vaginal examination showed that the uterus and adnexa were normal. There was a small cervical erosion with slight leukorrhea. There were moderate sized lymphatic glands palpable in the anterior cervical, axillary and inguinal regions. There was no clubbing of the fingers or cyanosis. Four plus pitting edema of both ankles was present. The cranial nerves were intact and there was no tremor present. Motor power was good. All deep tendon reflexes were 3 plus and equal. Superficial reflexes were normal. No abnormal pathologic reflexes were seen. Sensations were normal.

Laboratory studies revealed the following: Urinalysis on admission, pH 4.5; specific gravity, 1.015; albumin, 4 plus; glucose and acetone negative; microscopic examination showed frequent white blood cells, moderate red blood cells and frequent granular casts. Throughout the hospital stay the specific gravity ranged between 1.011 and 1.022, albumin was 4 plus, with moderate white blood cells, red blood cells and granular and hyaline casts. Urine revealed Streptococcus viridans on April 29, 1946; gamma streptococcus on May 7, 1946. Blood counts on admission: red blood cells, 2,430,000; hemoglobin, 7 Gm.; white blood cells, 5,000; polymorphonuclears, 73; transitionals, 3; lymphocytes, 19; monocytes, 2; eosinophiles, 3; slight hypochromia and poikilocytosis were noted on the blood smear and the platelets appeared to be increased. Throughout the hospital stay the red blood cells ranged between 2,350,000 and 3,450,000; hemoglobin between 7 Gm. and 8.5 Gm.; white blood cells between 4,200 and 5,000 until 21,800 on the day of death. There was little change in the differential blood counts except for an eosinophilia of 8 per cent on one occasion. Ninety-six per cent polymorphonuclear cells were seen on the day of death.

The blood cultures were sterile; the sedimentation rate was 69 mm. in one hour. Blood chemical studies showed that the non-protein nitrogen was 75 mg. per cent on admission and it rose to 112 mg. per cent; total protein, 4.8 Gm.; albumin ranged from 2.2 to 2.6 Gm.; globulin from 2.5 to 2.2 Gm.; cholesterol was 420 mg. per cent on admission and fell to 250 mg. per cent; cholesterol esters 143 mg. per cent; urea nitrogen from 45 to 56 mg. per cent; creatinine from 2 to 5 mg. per cent; sugar 118 mg. per cent; CO_2 combining power from 40 to 50 vols. per cent; serum calcium 12 mg. per cent. Blood Wassermann was negative. Phenolsulphonphthalein test showed 5 per cent excretion in fifteen minutes, 10 per cent in thirty minutes, 20 per cent in one hour, 35 per cent in two hours. Venous pressure in the right arm was 125 mm. of water and in the left arm 150 mm. of water. Circulation time with decholin was 14 sec. and with ether 7 sec. X-ray of the chest April 24, 1946, revealed that the heart was not enlarged in the transverse diameter. No enlargement of the left auricle was visible

upon barium swallow. There was small effusion in the horizontal fissure of the right lung. In May 13, 1946, there was pneumonic consolidation in the lower two-thirds of the right lung and in the middle third of the left lung. Electrocardiograms showed regular sinus rhythm, low voltage, left axis deviation and P-R interval of 0.16 seconds. Subsequent electrocardiograms showed a sinus tachycardia with no other diagnostic alterations.

For the first four days of the patient's course in the hospital her temperature was normal, but for the remainder of the patient's stay she ran a low grade remittent fever up to 101.8°F. Dyspnea at rest which was not present on admission became a prominent symptom after the second hospital day. The patient was treated for an acute exacerbation of chronic glomerulonephritis. In view of the chronic otitis media as a possible focus of infection a course of penicillin was given for eight days (20,000 units every three hours intramuscularly). The febrile toxic course continued and penicillin was discontinued. On the ninth hospital day swelling of the left hand, with pain in the left elbow and right hand, was noted. Fluid was found at both bases with occasional râles at the left base. A flame-shaped hemorrhage was seen in the retina, with narrowing of the retinal vessels. The previously heard systolic murmur was intensified and a diagnosis of acute rheumatic fever was entertained. Several observers noted an apical presystolic murmur. The patient received 80 gr. of salicylates a day. This medication was maintained for one week, to the point of mild toxicity, with no relief of pyrexia or joint manifestations. Two blood transfusions were given, with only temporary elevation of red count and hemoglobin. On two occasions the patient developed a chill and went into acute pulmonary edema while receiving intravenous infusions of Hartmann-Ringer's solution and blood plasma. The patient responded favorably to the usual emergency measures.

On the twenty-third hospital day the patient complained of precordial pain and a pericardial friction rub was heard at the apex. The diagnosis of acute rheumatic fever was reconsidered and salicylates were started again with no apparent effect. On the twenty-fourth day all the clinical and laboratory findings were reviewed. In order to fit the entire clinical picture into one pathologic entity the tentative clinical diagnosis of disseminated lupus erythematosus sine lupo was suggested, and the diagnosis of acute rheumatic fever was discarded.

The patient became severely dyspneic, orthopneic and cyanotic on the evening of the twenty-fourth day. Pulmonary edema developed but she responded fairly well to oxygen and intravenous aminophyline. On the twenty-sixth hospital day she again developed severe pulmonary edema, and the possibility of pericardial effusion with tamponade was considered. However, since the venous pressure was 130 mm. of water and the heart sounds were heard clearly, a pericardial tap was not considered advisable at that time. The blood pressure had ranged between 180/100 and 214/128, but on this day it was 144/92. She was given morphine, intravenous 50 per cent glucose and aminophyline, with little effect. On the twenty-seventh day pulmonary edema continued in spite of oxygen and the usual therapy. The heart sounds were well heard and not muffled. The pulse was rapid and regular. No pericardial rub could be heard. The cardiac dullness was enlarged to the left anteriorly and below the angle of the left scapula posteriorly. The liver was palpable and there was generalized edema. A phlebotomy of 325 cc. was performed, with some relief of the dyspnea. X-ray of the chest did not reveal any pericardial effusion. The patient was digitalized parenterally, with no apparent improvement. A positive pressure respirator was applied. A pericardial tap was attempted anteriorly and posteriorly, but no fluid was obtained. The patient continued in pulmonary edema despite energetic therapy and became unconscious while in the positive pressure respirator. She expired on May 14, 1946, the twenty-seventh hospital day.

* At autopsy the gross findings were as follows: The body was that of a thirty-four year old white woman, 162 cm. in length, and weighing approximately 135 pounds. The skin was quite pale. No petechiae were seen. Pitting edema of both ankles was present.

The peritoneal cavity contained about 100 cc. of clear, pale yellow fluid. The peritoneal surface was smooth and glistening. The edge of the liver extended 2 cm. below the right costal margin in the mid-clavicular line. The right pleural cavity contained 75 to 100 cc. of clear, light

* We are grateful to Dr. Stanley Gross of the Department of Pathology, Bellevue Hospital, New York, N. Y., for the complete autopsy protocol.

FIG. 1. Photograph of the heart showing verrucae on the mitral valve.

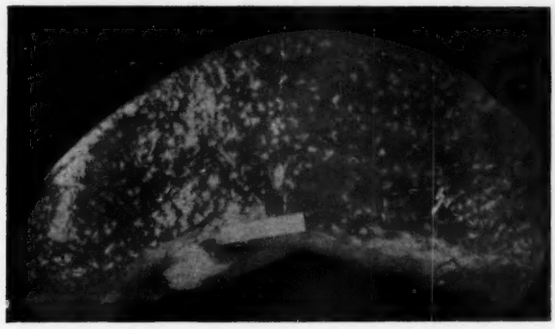


FIG. 2. Photograph of spleen showing malphigian bodies as prominent small grey nodules.

yellow fluid. The lung lay free in the pleural cavity. The left pleural cavity contained 75 to 100 cc. of bloody fluid. The left lung lay free except for one firm adhesion between the parietal wall and the posterior portion of the left upper lobe. On the outer surface of the parietal pericardium there was a pinpoint hemorrhage and blood clot, without evidence of perforation of the pericardium or myocardium. There were a few pleuropericardial adhesions on the left. The pericardial cavity contained 75 cc. of cloudy, grey fluid. Thin, long strands of fibrin were seen floating in the fluid and a few strands extended from the visceral to the parietal pericardium.

The heart weighed 420 Gm., but did not appear dilated. The pulmonary artery contained only postmortem clots. Both auricles were of normal size and the auricular appendages were clear except for postmortem clots. The tricuspid valve leaflets were thin and delicate and the chordae tendineae were long and thin. The mitral valve leaflets were thin and fairly delicate. On the auricular surface of the aortic leaflet of the mitral valve near the free margin there were two small pinhead-sized verrucae which appeared greyish white to yellowish white in color and were firmly attached. (Fig. 1.) A few chordae tendineae appeared to be slightly thickened but there was no fusion or shortening. The aortic valve leaflets were fine and delicate. The myocardium was firm and pinkish in color. No areas of fibrosis were seen. The coronary arteries were patent throughout, were not tortuous and the walls were not sclerotic. There was some mottling of the intima by pinpoint yellow atheromatous deposits, particularly in the right coronary artery and the initial portion of the left coronary artery. The right ventricular wall was somewhat hypertrophied and thickened. Culture of the heart's blood taken at autopsy was sterile. There were many pinpoint intimal deposits of yellow material in the arch and ascending portions of the aorta.

The left lung weighed 790 Gm., the right lung weighed 940 Gm. The right lung was subcrepitant throughout and was firm. The pleura over this lung was smooth. The cut surface of both upper and lower lobes appeared somewhat brownish. The parenchyma was somewhat airless and frothy fluid was expressed from the cut surface. The bronchi contained frothy fluid but the mucosa appeared normal. The left lung was fairly firm throughout and quite firm in the region of the fibrous adhesions. In this area the lung surface was puckered and a deep scar was evident. Over the lateral surface of the lower lobe was seen a small area covered by a loosely adherent blood clot. The cut surface of the left lung showed a few scattered areas of consolidation which felt firmer than the surrounding tissue but did not stand out from it. The bronchi were as described in the right lung. Hilar and tracheal-bronchial nodes appeared slightly enlarged and succulent and on section showed a grey-black color.

The liver weighed 1,630 Gm. Mild congestive changes were present; otherwise, the liver was not remarkable.

The spleen weighed 230 Gm.; the surface was smooth, the capsule was thin and the organ appeared pinkish-grey. The cut surface was flat and malpighian bodies stood out prominently as small grey nodules each about 4 mm. in diameter. (Fig. 2.) The trabeculae were not prominent. The splenic pulp was somewhat firmer than usual. There was a small accessory spleen about 1 cm. in diameter in the gastrolienal ligament.

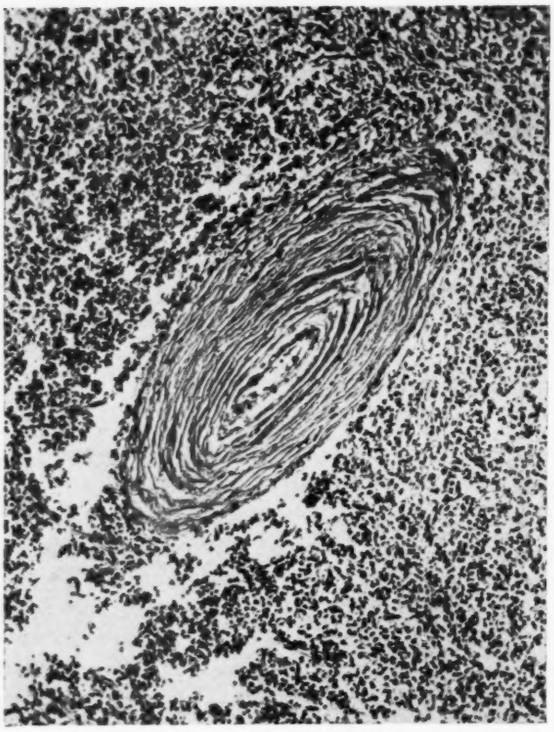


FIG. 3. Spleen showing periarterial fibrosis ("onion skin"); hematoxylin and eosin stain, × 220.

The right kidney weighed 280 Gm. and the left kidney weighed 250 Gm. Both kidneys were very large, pale and soft and closely resembled a "large white kidney." The capsules stripped with ease and smooth, grey-white waxy surfaces were seen. There were a few thin red streaks mottling the surface. On section the surface of the kidney did not bulge and appeared pale, waxy and yellow. The cortex on the right was 7 mm. wide and on the left 5 mm. wide. Cortical-medullary differentiation was fairly distinct. The pelves and ureters appeared normal.

Axillary, inguinal, retroperitoneal, posterior mediastinal, cervical and mesenteric lymph nodes were all enlarged. The nodes were soft, succulent, discrete and on section the surface bulged slightly and appeared pink-grey.

The vertebral bone marrow was pale pink throughout; the bony architecture appeared normal.

The neck organs were essentially normal except for mild edema of the arytenoid region. The thyroid was normal in consistency and on section showed a gelatinous shiny surface. Two parathyroids were identified and appeared grossly normal.

The pancreas, adrenals, gallbladder, biliary ducts and urinary bladder were all grossly normal.

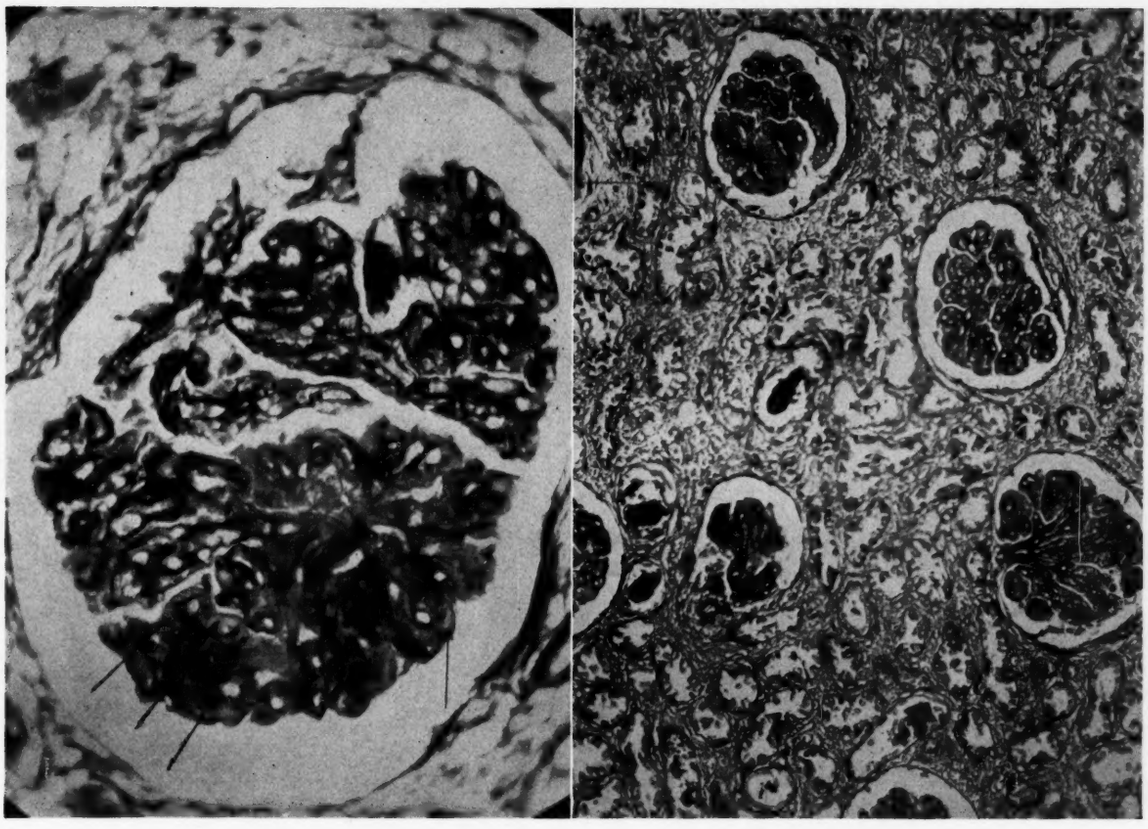
The genital tract was not remarkable except for several small, simple cysts of the ovaries.

Mild congestive changes were present in the gastrointestinal tract; otherwise, it was normal.

The dura of the brain was smooth and glistening. The leptomeninges were thin and delicate. The brain weighed 1,180 Gm. The middle ear on the right was opened and a small amount of serous fluid was seen. On the left the middle ear revealed a moderate amount of glairy fluid. The brain appeared normal to the naked eye and no microscopic sections were taken.

Microscopic findings revealed the following: The auricular and ventricular endocardium of the heart showed no significant changes. The myocardial fibers had distinct cross striations and occasional fibers had small vacuoles. There was a slight increase in connective tissue around occasional blood vessels but no marked cellular response was found. No Aschoff bodies were seen. The mitral valve leaflet, in the distal third, revealed a flat thickening of the endocardium and subendocardial connective tissue on the auricular surface. This thickening was composed of hyaline material. Occasional clumps of pink-staining collagenous material appeared deeply eosinophilic but not smudgy. The pericardium showed changes consistent with the pericarditis described in the gross findings. The serous lining was thickened and a few cells were deep in places. The tricuspid valve leaflet showed no significant changes.

Both lungs showed similar pictures. Many alveoli contained and some were filled with an exudate made up of red cells, fibrin, polymorphonuclear cells, large mononuclear cells, some with reniform nuclei, and other large mononuclears with brown granular pigment. Some alveoli contained moderate to marked numbers of pigment-bearing macrophages. Some alveoli contained edema fluid and in some cases were partially lined by hyaline eosinophilic material. Some of the septal walls were infiltrated by polymorphonuclears and mononuclears. There was moderate congestion throughout the bronchial and bronchiolar walls. The small vessels, particularly capillaries and venules, showed a lifting of the endothelium and there was some pink fibrinoid material deposited beneath. The larger vessels did not show marked changes. The left pleura of the



4 5

FIG. 4. Thickening of the basement membrane of glomerular loop by hyaline material with "wire-loop" formation; azancarmine stain, × 550.

FIG. 5. Photomicrograph of kidney showing wire-loop formation, glomerular crescents, intercapillary sclerosis and atrophic tubules occasionally filled with hyaline casts; azancarmine stain, × 220.

lung was slightly thickened and there was fibrin deposited on the surface.

In the spleen the malpighian bodies were cellular and stood out because of the peculiar configuration of the central arterioles. These vessels, the smaller arterioles in the red pulp and some of the arteries in the trabeculae were ringed by pink concentric lamellae which stained blue with azancarmine and produced an "onion-skin" appearance. (Fig. 3.) In addition, there was deposition of pink-staining material subintimally in some of these vessels, particularly the smaller arterioles. The sinusoids were moderately distended and congested. The endothelium was fairly prominent. An occasional megakaryocyte was seen and there were small collections of large mononuclears. Occasional polymorphonuclears and eosinophiles were seen in the sinusoids as well as some brown pigment-bearing macrophages. Large and small veins showed diffuse and focal infiltration of the intima with small and large mononuclears.

Sections of the kidney showed marked alteration of all structural elements. The glomeruli were often swollen and appeared larger than normal. Many were markedly anemic and a rare one was congested. The glomerular loops were often simplified and some had adhesions binding them to a thickened Bowman's capsule. Of note was the thickening of the basement membrane of some glomerular loops by deep pink-staining hyaline material. The appearance of these loops was suggestive of the so-called "wire loop" lesion, (Fig. 4) and with azancarmine this hyaline material stained red or occasionally reddish blue. These glomeruli also showed nuclear fragmentation. Occasionally, there was some evidence of intercapillary sclerosis. Bowman's capsule was often thickened by crescent formation. (Fig. 5.) Many of these were epithelial but often they were made up of fibrous tissue. These crescents and the thickened capsule stained blue with azancarmine. Many of the tubules were atrophic and lined by

flattened epithelium. Some tubules were filled with hyaline casts. Groups of tubules were dilated and filled with smudgy, deeply eosinophilic casts. There was a diffuse increase in loose connective tissue and focal areas of fibrosis were seen. A moderate number of small arterioles and medium sized arteries showed some intimal thickening which stained blue with azancarmine. Fat stain showed scattered granules of red-staining material in glomerular cells, in tubular epithelium and occasionally in hyaline casts.

The lymph nodes showed reticulo-endothelial hyperplasia.

The bone marrow was quite cellular and appeared moderately to markedly hyperplastic.

The pancreas was normal microscopically and the vessels showed no remarkable changes.

PATHOLOGY

Lupus erythematosus disseminatus affects the kidneys in such a high percentage of cases that this feature may be regarded as an integral part of the disease.[2]

The diversity of pathologic renal findings is very striking. Mallory[3,4] described kidney changes as very minimal; an occasional glomerulus showed glomerulitis of a tuft or a portion of a tuft and the convoluted tubules were a little swollen. Nephritis was diagnosed in 70 per cent of his cases. Stickney and Keith[5] described fifteen cases, eight of which showed no definite change other than that seen terminally in debilitating diseases. They found a proliferation of the endothelial cells of the glomerular capillaries with hyaline thickening of these capillary walls and an irregularity and thickening of the basement membrane. They regarded these changes as somewhat similar to those found in acute glomerular nephritis[6–8] and the toxemias of pregnancy. The lesions were considered secondary to the toxic processes and did not represent primary renal disease. Keith[9] summarized the renal findings as follows: "Renal insufficiency does not play an important role causing death, since chronic uremia very seldom occurs. The histologic changes in the kidneys are almost never as extensive as those seen in progressive glomerulonephritis of similar duration. The usual renal lesions, particularly those of the glomerulus, may resemble lesions found during the first two weeks of acute glomerulonephritis. But in lupus erythematosus renal anomalies such as albuminuria, cylindruria, and microscopic hematuria may persist for two or three years in contrast to a few weeks in the former condition and yet similar histologic findings be present. This fact suggests that the renal threshold in lupus erythematosus is a mild reaction to a toxic agent with minimal scar formation. Further study has indicated that this renal lesion is non-specific and can be produced in various toxic conditions as for example, lupus erythematosus, ulcerative colitis, and peritonitis. In some of these cases were found albuminuria varying periodically from grades 1 to 4 and at necropsy only minor histologic changes in the glomerulus. Such findings suggest that the renal lesion may be temporarily reversible and analogous to what sometimes occurs in the skin lesions."

Baehr, Klemperer and Schiffrin[10] first described the "wire-looping" in the glomerular tuft due to a peculiar thickening of the walls of the glomerular capillaries which did not contain amyloid or lipoid material. Along with these changes they described proliferative and thrombotic processes involving part or all of the glomerular vasculature; the picture might resemble that of the embolic glomerulonephritis seen in subacute bacterial endocarditis.[11,12] Klemperer, using the Mallory connective tissue stain, believes that the wire loops indicate a fibrinoid degeneration and collagenization of the basement membrane. This wire-loop appearance was not constant, but they claimed to be able to distinguish the wire-loops in lupus erythematosus from those occurring in eclampsia, renal amyloidosis and malignant nephrosclerosis. However, they stated that the morphologic aspects of fully developed vascular necrosis obtaining in accelerated arteriosclerosis and in lupus erythematosus are indistinguishable. Mallory[3] was able to find the wire looping in

only one-half of the patients at the Massachusetts General Hospital. Baehr, Klemperer and Schiffrin[10] in their original description said: "The wire-looping lesion was not seen in any other human disease, except perhaps eclampsia." They also mentioned the glomerular and vascular lesions described by Wadsworth in horses which had been immunized by repeated intravenous injections of live bacteria especially of the pneumococcus and streptococcus group. Baehr et al.[10] found hypertension relatively uncommon, whereas Rose and Pillsbury[13] found hypertension in approximately one-half of their patients. Of those that came to necropsy (five cases) none had hypertension but they did show the wire-loop appearance of the glomerular capillaries, focal necrosis and varying degrees of cellular proliferation, avascularity and ischemia. No gross characteristics were seen in the kidneys. The pathologic diagnosis was focal glomerulonephritis in three patients and atypical diffuse glomerulonephritis in two. Cloudy swelling, abscess and simple nephrosis were the other changes found.

In our patient the outstanding renal pathologic features were the large white kidneys, swelling and congestion of many glomeruli, numerous wire-loops in the glomerular capillaries, some interstitial sclerosis, crescent formation, atrophic and dilated tubules with hyaline and eosinophilic casts, focal areas of fibrosis and occasional intimal thickening of the small arterioles and middle-sized arteries. Fat stain showed scattered granules of red-staining material in glomerular cells, in the tubular epithelium and occasionally in hyaline casts.

Another important pathologic finding in this patient was the periarterial fibrosis in the spleen. Klemperer, Pollack and Baehr[14] were of the opinion that the periarterial sclerosis found in nearly every case is so arresting that it must be considered specific. Kaiser,[15] however, has shown that these lesions are not specific for lupus erythematosus, and occur in other widely dissociated diseases. He found periarterial fibrosis of the spleen in 3.2 per cent of his control series and in approximately 85 per cent of the proven cases of lupus erythematosus. His conclusions, while against the specificity of this lesion, do not oppose its use as a positive diagnostic finding when used in conjunction with the clinical history and other pathologic findings.

COMMENTS

The sine lupo element of this disease picture was first stressed by Gross and Friedberg[1] in 1936. In their analysis of forty-seven cases (previously reviewed by Baehr, Klemperer and Schiffrin in 1935[10]) of non-bacterial thrombotic endocarditis they found seven cases, all women, which very closely resembled both the atypical verrucous endocarditis of Libman and Sacks[16] as well as disseminatus lupus erythematosus, except that no skin lesions were found.

Keil in 1940[2] established his criteria of sine lupo in the following three categories: (1) Rheumatoid arthritis with sensitivity to sunlight and involvement of the kidneys and serous membranes;[17] (2) febrile thrombopenic purpura with negative blood culture and renal involvement;[18] (3) polyserositis with widespread involvement of other systems including the kidneys.[19,20]

Rose and Pillsbury consider the lupus erythematosus disseminatus sine lupo diagnosis in the presence of fever, leukopenia, petechia or purpura, arthralgia, endocarditis, pericarditis, pleural effusion, renal injury and sterile blood cultures.

Friedberg, Gross and Wallach[19] in 1936 described four cases of lupus erythematosus disseminatus sine lupo characterized by onset of acute polyarthritis, pleuritis, pericarditis and negative blood cultures. The fever was prolonged and all four patients showed evidence of nephritis. Only one revealed any evidence of renal insufficiency. Myocardial insufficiency was not a clinical feature.

It was previously thought that toxic products originated in the skin and were then dispersed throughout the internal

organs, giving the pathologic changes of disseminated lupus. However, numerous cases of disseminated lupus were reported in which the visceral symptoms antedated cutaneous manifestations by varying periods. In addition, very often in terminal cases of this disease the eruption disappeared entirely.[17] In Stickney and Keith's[5] paper in 1940, two patients of fifteen had albuminuria before cutaneous symptoms, suggesting that the skin lesion does not necessarily appear before dissemination of the disease.

The other unusual feature of this case was the presence of a nephrotic syndrome associated with hypertension and azotemia. Brooks[21] in 1895 described a case of disseminated lupus erythematosus in a thirty-three year old woman whose kidneys postmortem showed "soft white swelling." In Stickney and Keith's[5] series of fifteen cases there was one that had some evidence of subacute or early chronic glomerular nephritis. In all of their fifteen cases the kidneys were either normal or greater than normal in weight. Keil[2] in 1940 stated that he encountered several instances of disseminated lupus erythematosus in which the clinical features simulated the nephrotic phase of glomerulonephritis with moderate elevation of blood pressure.

Lupus erythematosus disseminatus has been considered a systemic disease of unknown etiology, with clinical and laboratory findings that indicate involvement of many organs. The intensity of signs and symptoms in any one system is unpredictable. The skin may be spared occasionally, as in our case, thus making the term lupus erythematosus, which implies a skin disease, a misnomer. Likewise, the term lupus is inaccurate since the tuberculous etiology has been disproven. The endocardium may be spared and therefore every case need not have a Libman-Sacks component.

The general pathologic findings are as variable as the clinical manifestations. The widespread collagen involvement with focal distribution is not specific since it also occurs in other systemic diseases such as rheumatic fever, periarteritis nodosa, scleroderma and dermatomyositis. The wire looping of the glomerular capillary and the periarterial fibrosis ("onion peel") of the spleen has been mentioned. The renal pathologic picture is non-specific and diverse, ranging from minimal to widespread damage.

Most clinical entities are established and authenticated by pathology; however, this does not hold true for lupus erythematosus disseminatus because the pathologic changes are non-specific. Therefore, the diagnosis can be determined only by correlation of the various system involvements and the exclusion of other symptom-complexes. As Reifenstein[22] states the clinical features together have a fairly characteristic grouping but, considered individually, show much variation. The above views are in keeping with the teachings of the late Soma Weiss.[23,24]

The clinical diagnosis of lupus erythematosus disseminatus sine lupo in our patient was made because of the long-standing and remittent arthritis, prolonged intermittent fever with sterile blood cultures, leukopenia and anemia, generalized lymphadenopathy, systolic and questionable diastolic murmur, polyserositis and a gradual downhill course. This entire symptom-complex was superimposed upon what resembled the nephrotic phase of chronic glomerulonephritis. The renal picture with hypertension and azotemia was unusual.

The clinical impression was strengthened by the pathologic findings of polyserositis, atypical verrucous endocarditis, lymphadenopathy, large white kidney with wire looping, periarterial fibrosis of the spleen and the absence of lesions associated with rheumatic fever.

SUMMARY

1. A case of lupus erythematosus disseminatus, without skin manifestations (sine lupo), is presented and the autopsy findings are described.

2. Other interesting features of the case are the nephrotic component, hypertension and renal insufficiency.

3. The literature is reviewed in reference to these unusual features.

4. The relationship of the clinical picture to the pathologic condition in this syndrome is discussed.

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Hemolytic Staphylococcus Albus Bacteremia and Pericarditis Treated with Sodium Salt of Penicillin and Penicillin in Beeswax and Peanut Oil

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USE of the sulfonamide drugs for the past few years in treatment of staphylococcic bacteremia and staphylococcic infections has proven ineffective for the most part. However, since the advent and development of penicillin preparations, prognosis in these diseases has been immeasurably improved. The drug has proved itself of inestimable value in the prevention and active therapy of metastatic abscesses which are a constant threat in staphylococcic bacteremia. Penicillin suspended in peanut oil and beeswax, as developed by Romansky, is finding progressively wider application. He has demonstrated that adequate and prolonged concentrations of the drug may be maintained in the blood serum after a single injection of 300,000 units contained in 1 cc. of the mixture, using the intramuscular route. The efficacy of this preparation in the treatment of gonorrhea and syphilis by single daily injections has been established. Several cures of subacute bacterial endocarditis have been reported during use of penicillin-beeswax-oil mixture. However, no reports of its use in acute staphylococcic bacteremia have been noted by the author. The therapeutic problem in this type of infection is to maintain adequate serum concentrations of the drug to render the blood stream sterile as quickly as possible, thereby preventing development of metastatic abscesses, purulent pericarditis and/or other possibly fatal complications of the disease. This desired serum concentration, of course, will vary with the susceptibility of the organism to the drug.

It is the purpose of this paper to report a case of a patient with acute staphylococcal bacteremia who developed metastatic abscesses and pericarditis with congestive heart failure. He was successfully treated by the use of both the sodium salt of penicillin and penicillin in beeswax and peanut oil. At the time of the patient's illness a method for determination of serum penicillin concentration was not available in this hospital. It was thought, therefore, that both dosage forms of the drug should be used in order to produce promptly and maintain a serum penicillin level well above the theoretical concentration to which the organism was susceptible.

CASE REPORT

A twenty-three year old, white soldier was admitted to the Station Hospital, Camp Hood, Texas, September 17, 1946, complaining of severe pain in the right hip. Seven days prior to admission he had noted a "catch" in his hip which progressed over the next few days to a steady, dull ache with radiation to the right knee on weight bearing. This was followed by the occurrence of chills, fever and sweats each night until his admission. He had superimposed generalized aches and pains, weakness, anorexia and fatigue.

The patient had lost about 30 pounds over a three-year period of time but had had no accompanying fatigue, nervousness or asthenia. He had gonorrheal urethritis in 1942 and 1943 and had had urethral sounds passed in 1943 about

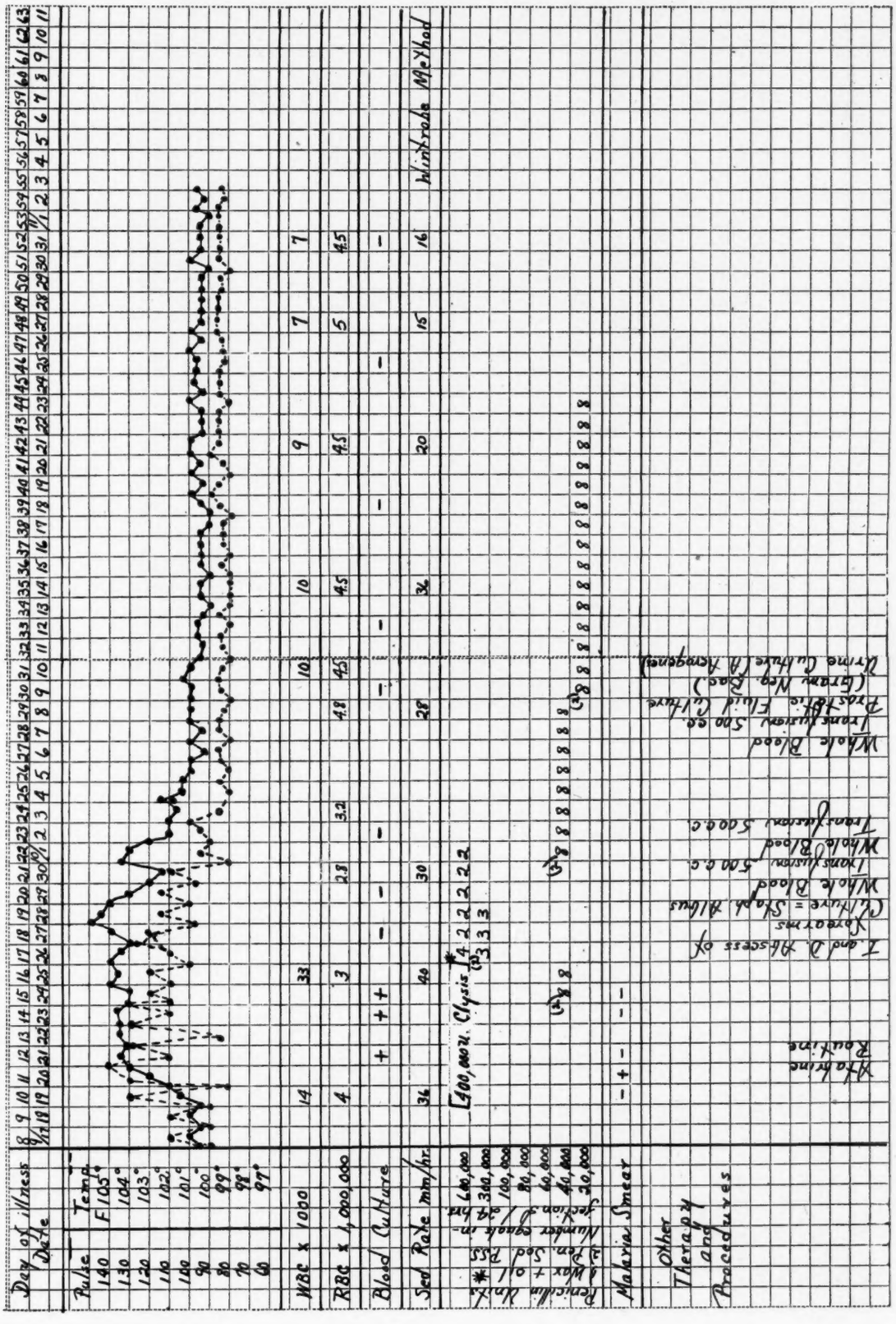

FIG. 1. The patient's clinical course in the hospital.

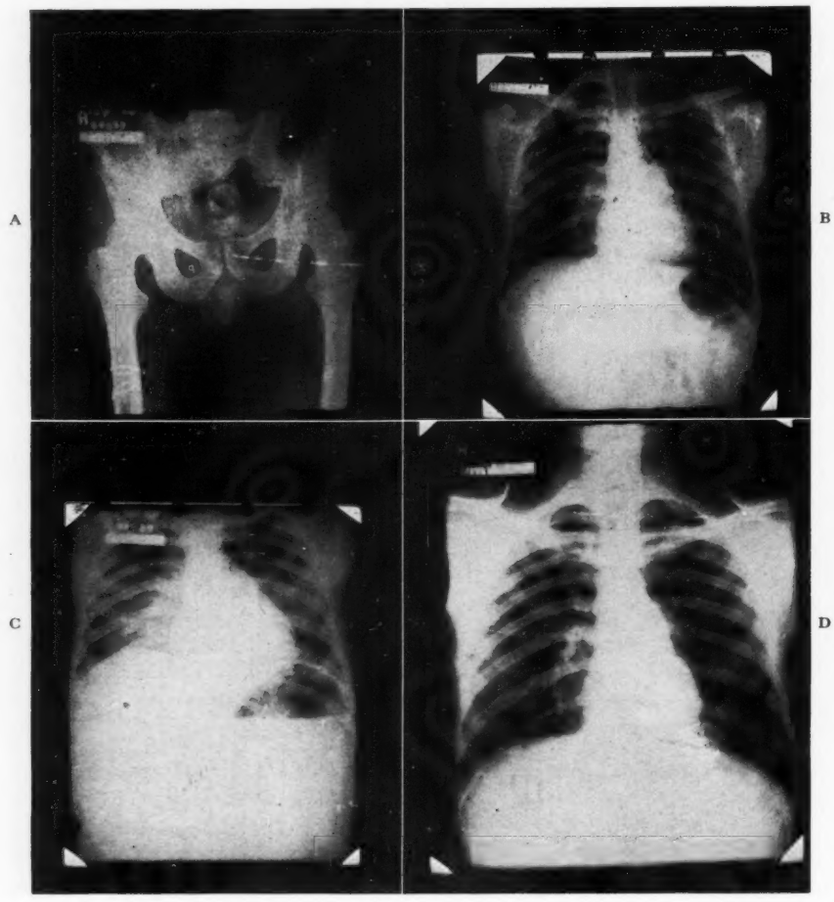

FIG. 2. A, the metallic rings encircling the femur may be seen. No evidence of osseous pathologic change. B, normal except for the slight mitral configuration. C, film during episode of congestive failure. Heart shadow is somewhat enlarged and there is some "straightening" of the left border; there is evidence of congestive phenomena in the lung fields. D, film following recovery; a nearly normal configuration with the exception of some prominence of the pulmonary conus segment.

four months following the second episode of urethritis. There was a history of mild, chronic alcoholism. The family history was non-contributory. His past medical history disclosed that a compound fracture of the proximal third of his right femur had occurred at the age of nine years. This was treated by open reduction and surgical "wiring."

Physical examination revealed a chronically ill patient who had a temperature of 99°F., pulse rate of 110 per minute, respiratory rate of 18 and blood pressure of 110/60. There was moderate pallor. The heart and lungs were clinically normal. Equivocal tenderness over a large surgical scar on the lateral aspect of the right leg was noted.

Laboratory examination revealed the following: Blood: hemoglobin, 13 Gm.; leukocyte count, 14,000 per cu. mm.; polymorphonuclears, 88 per cent; lymphocytes, 12 per cent. Sedimentation rate, 34 mm. in one hour. Kahn test, negative; a blood smear (thick) for malarial parasites, negative. Urinalysis: a trace of albumin and 8 to 10 leukocytes per high power field. An electrocardiogram revealed only sinus tachycardia. X-ray film of the right hip and proximal femur disclosed an old, well healed fracture through the proximal one-third of the shaft of the right femur. Two metal wire loops encircled the femur at this site.

For the first two days following the patient's admission no definite diagnosis was reached and he began to manifest a high, spiking temperature. He was treated with only the usual analgesics. On September 20, 1946, a blood smear was reported positive for Plasmodium

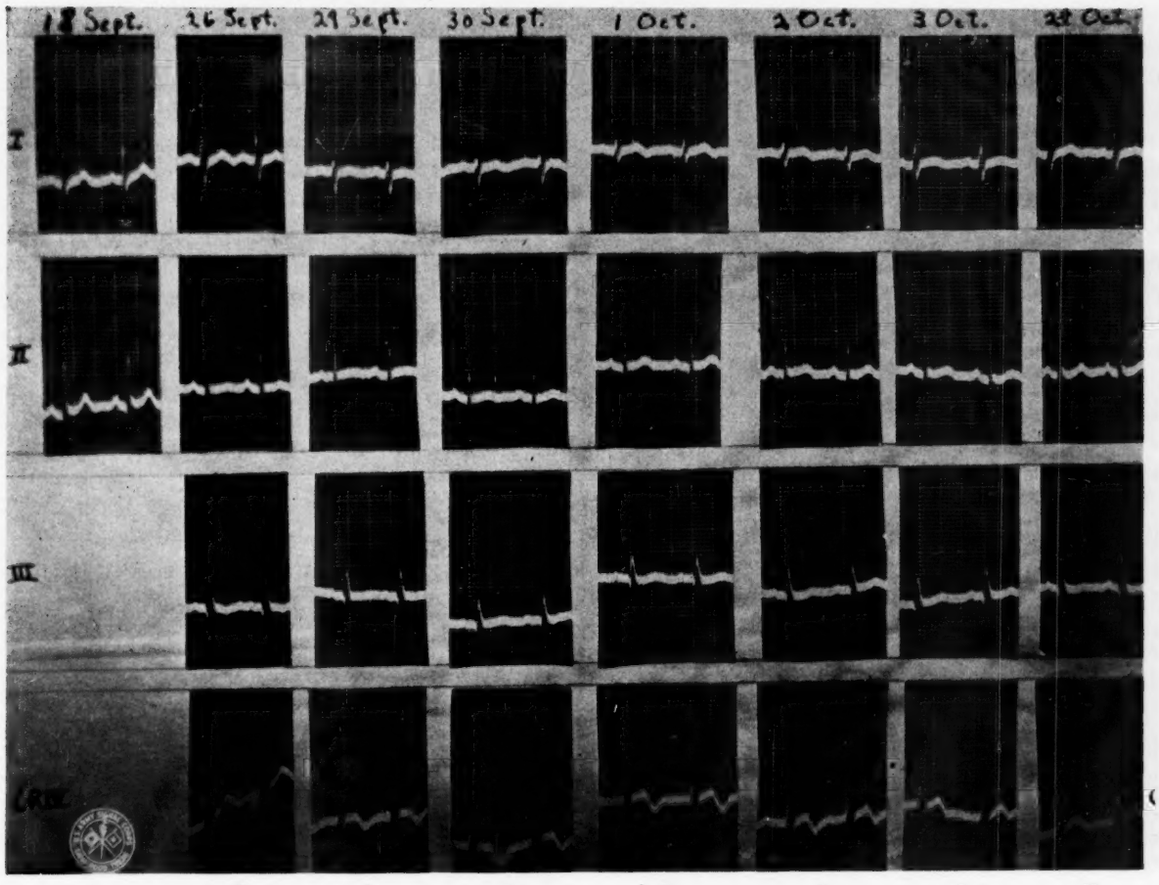

FIG. 3. A, leads I and II normal. B, there is slight widening of the QRS complexes and flattening of T_2. T_3 is inverted. C, there is decreased voltage of all the complexes, flattening of T_1, T_2 and T_3 and deep inversion of T_4. S_1 has become prominent. D, further decrease in voltage of all the complexes is noted. T_1 and T_2 are diphasic and there is deeper inversion of T_4. E, F and G, amplitude of all complexes is slowly increasing and the T waves are returning to a more normal configuration. H, this tracing is within normal limits as have been all subsequent tracings. There were no significant S-T segment changes noted in the series presumably because the pericarditis was rather slow in onset.

vivax and routine atabrine therapy was instituted. He did not improve, the temperature was unaffected and he continued to complain of pain in his right hip and proximal femur. On September 23, 1946, swollen, hot, edematous areas were noted on the dorsal aspect of both forearms which rapidly progressed to a fluctuant state. On September 24, 1946, a blood culture was reported positive for hemolytic staphylococcus albus.

Laboratory findings revealed the following: Blood: hemoglobin, 11 gm.; erythrocytes, 3,000,000; leukocytes, 33,100; polymorphonuclears, 92 per cent; lymphocytes, 8 per cent. X-ray films of the forearms showed no bone abnormality. A film of the chest disclosed singular prominence of the pulmonary artery conus segment. Blood urea nitrogen was 14 mg. per cent and the carbon dioxide combining power was 68.3 volumes per cent.

Penicillin therapy was instituted using 40,000 Oxford units of the sodium salt intramuscularly. Incision and drainage of the forearm abscesses was accomplished and a large quantity of thick, purulent material was evacuated. Culture of the pus revealed Staphylococcus albus. Sensitivity to penicillin, streptomycin and sulfadiazine were tested by Levine's modification of the technic. The organism was found to be inhibited *in vitro* by penicillin concentrations of 0.40 units per 100 cc. and by streptomycin concentrations of 14.0 micrograms per 100 cc. It was not affected by sulfadiazine.

The veins of the arms were inaccessible because of gross infection and so a continuous hypodermoclysis of normal saline, 1,000 cc. with

400,000 units of penicillin sodium every eight hours, was given. Penicillin in beeswax and peanut oil was started using the technic of preparation and injection described by Geiger and Goerner. The 40,000 unit dosage of penicillin sodium was discontinued September 25, 1946, and the penicillin-beeswax-oil mixture was begun and continued for five days, using a dosage of 600,000 units intramuscularly every six hours for four doses and then 600,000 units every twelve hours. Two subsequent blood cultures were positive as seen on the clinical chart. (Fig. 1.) An electrocardiogram on September 26, 1946, disclosed a decrease in the amplitude of the T waves in all leads and slightly decreased voltage of all complexes.

On September 28, 1946, the patient became progressively dyspneic and orthopnea developed over a twelve-hour period of time. The neck veins became distended and the liver could be palpated two finger breadths below the right costal margin. It was acutely tender and its edge was rounded. The lung fields at first showed dry inspiratory and expiratory râles which rapidly became moist and bubbling in type. The point of maximum impulse of the cardiac thrust was in the fifth interspace 12 cm. to the left of the mid-sternal line. A gallop rhythm was present. The apical rate was 130 per minute. Paradoxic pulse was not present. A friction rub, best heard at the end of expiration, was noted and was interpreted as being pericardial in origin. A 3 plus pitting edema of the presacral area was demonstrated. The blood pressure was 130/90.

Diagnosis of acute pericarditis with right and left ventricular failure was made. The electrocardiogram disclosed low voltage of all the complexes, flattening of the T waves in the classical leads and definite inversion of T_4. A chest x-ray film demonstrated definite increase in the size of the cardiac shadow and the mitral configuration was still present. (Figs. 2 and 3.)

The patient was treated with morphine sulfate, rapid digitalization using intravenous digifoline, and 1 cc. of mercupurin was given intravenously. With other supportive therapy, the patient again became well compensated in thirty-six hours and was placed on a maintenance dose of digitalis by mouth. All clinical signs of congestive failure disappeared and subsequent chest x-ray films showed a more normal cardiac silhouette. The electrocardiogram gradually returned to normal limits. The patient continued for many days to complain of pain in his right hip and femur but this finally disappeared. X-ray films of the hip joint, femur and knee failed to disclose any evidence of an osseous pathologic lesion.

The patient's subsequent clinical course was uneventful. The friction rib was no longer audible on October 4, 1946. The patient finally became afebrile October 21, 1946, and has continued so. The penicillin dosage was gradually reduced and finally discontinued as indicated on the clinical chart. There were no ill effects and all subsequent blood cultures have been negative. The patient has returned to duty, gained weight, has no complaints and appears in good health three months after the onset of illness.

COMMENTS

Because of the high mortality of patients with staphylococcic bacteremia complicated by metastatic abscesses and pericarditis, this patient's case was believed to be worthy of report. Use of penicillin in beeswax and peanut oil to produce and maintain a high serum concentration of the drug in acute overwhelming infections is thought to be worthy of further trial in selected cases. Sensitivity determinations should be carried out as well as serum penicillin concentrations whenever possible.

The focus of this patient's bacteremia was never established. Because of the roentgenographic mitral configuration, the possibility of chronic mitral valvulitis with endocarditis was entertained. However, in the absence of a suggestive history and a significant cardiac murmur this conjecture was discarded. The urinary tract did not seem a likely source. The history of a compound fracture of the right femur at the age of nine years coupled with the intense pain accompanying this illness strongly suggests the diagnosis of a chronic, dormant, low grade osteomyelitis of the femur reactivated during a period of general lowered resistance and a malarial parasitemia. This possibility, unfortunately, was not proven.

The development of acute pericarditis and congestive heart failure leads one to believe that the infecting organism had involved the pericardium and epicardium.

The clinical picture and electrocardiographic changes provide unequivocal evidence of myocardial involvement by the inflammatory process. It was believed that the high constant serum penicillin concentrations prevented occurrence of a purulent pericarditis. At no time did it seem clinically feasible to perform pericardial paracentesis; therefore, this opinion must remain conjectural. This patient's rapid recovery from a staphylococcal bacteremia with metastatic abscesses and pericarditis and the paucity of reports of patients treated in the manner outlined, makes this case significant.

CONCLUSIONS

(1) A case of staphylococcus albus bacteremia complicated by peripheral metastatic abscesses of the forearm and acute pericarditis accompanied by congestive heart failure is described. Complete recovery was accomplished using penicillin sodium in conjunction with penicillin in beeswax and peanut oil.

(2) Penicillin sodium was used subcutaneously and intramuscularly and penicillin in beeswax and peanut oil was given intramuscularly. In the opinion of the author the high penicillin concentration was responsible for the cure of the infection and prevention of development of a purulent pericarditis and other metastatic abscesses.

(3) The treatment followed seems worthy of further trial in similar cases requiring a high serum penicillin concentration because of massive infection and/or a resistant organism.

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Congenital Dextrocardia Complicated by Hypertension, Coronary Artery Disease and Myocardial Infarction*

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CONGENITAL dextrocardia associated with coronary artery disease is rare as judged by reports in the literature. Crawford and Warren[1] described a fifty-eight year old male who had congenital dextrocardia, a history of severe prolonged substernal pain associated with numbness in the right arm and the anginal syndrome upon effort. An electrocardiogram taken several months later and interpreted with the arm lead wires reversed was consistent with posterior wall infarction. Manchester and White[2] reported the case of a sixty-seven year old male with dextrocardia complicated by hypertension, coronary artery disease and the anginal syndrome. An electrocardiogram showed an abnormal T_1 prominent Q_2 and Q_3 and inverted T_4. There were no QRS changes in a single precordial lead. Geeslin and Tyler[3] took serial electrocardiograms on a forty-three year old male with dextrocardia following myocardial infarction. The changes were typical of anterior wall infarction. CF_2, CF_3 and CF_4 of the precordial leads were taken over the right side of the chest. The limb leads were interpreted with the arm lead wires reversed. Cain[4] found the electrocardiogram of a thirty-three year old male with congenital dextrocardia and the anginal syndrome to be normal except for left axis deviation. Interpretation was made with the arm lead wires reversed.

Ogaard, Voorhies, Burch and Cordill[5] recorded electrocardiograms on seven persons with congenital dextrocardia. Multiple precordial leads of the CF series, when taken over the right side of the chest, were found to be comparable to precordial leads from the left side of the chest when the heart is in normal position. One child, age fourteen years, showed T wave changes over the right ventricle, and one adult subject with hypertension showed T wave changes in each of the precordial leads. Q waves present in positions 5 and 6 in three subjects were of small amplitude; the largest was only 2.4 mm. in depth.

That the electrocardiogram in congenital dextrocardia can be interpreted by the usual criteria if viewed or taken with the arm lead wires reversed is further substantiated by the instance reported by Willius[6] of a fifty-nine year old male with hypertension. The electrocardiogram disclosed the RS-T segment and T wave deflection in opposite direction to the QRS complex in lead I representing the pattern of "left ventricular strain."

CASE REPORT

D. S. S., a seventy-three year old white married male farmer, was admitted to Duke Hospital on May 30, 1947, because of four episodes of substernal pain radiating to the right arm during the preceding two weeks. His past history was interesting in that he had had pneumonia in 1937 and was hospitalized for two

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months. He was informed at that time that his heart was in the right side of his chest. His health remained excellent until two weeks before admission when, while plowing, he developed sudden, severe, substernal pain with radiation to the right arm. Plowing was continued until the pain became so severe that he was forced to sit down; the pain lasted approximately one hour and was associated with sweating. The following day while walking home from town, a similar episode of pain developed which was partially relieved by rest. He continued home but was forced to stop several times because of exacerbations of the pain. Upon arriving home his physician administered a hypodermic and prescribed some capsules which relieved his pain. Physical activity was limited upon the advice of his physician and no further episodes of pain were encountered during the following week.

Six days before admission while sitting in a chair at home, he developed his most severe episode of substernal pain which was accompanied by nausea, vomiting and sweating. The pain lasted one hour until relief was obtained from a hypodermic. He then remained in bed until his admission to the hospital. Substernal pain returned on only one occasion, the night before admission; relief was obtained immediately by dissolving nitroglycerin beneath his tongue.

The temperature was 37.4°C., the pulse rate was 68 beats per minute and respirations were 20 per minute. Blood pressure was 128 mm. Hg systolic and 70 mm. Hg diastolic. Examination revealed a well developed and well nourished white male who appeared younger than his stated age of seventy-three years. Eyes, ears, nose, mouth and throat showed only mild sclerotic changes in the optic fundi; the two remaining teeth were carious and the tonsils were moderately enlarged. There was no distention of the neck veins. The lungs were clear. Examination of the heart disclosed the point of maximal impulse 8 cm. to the right of the midsternal line in the fifth interspace at the midclavicular line. The rhythm was regular. The sounds were of normal intensity but the second sound at the base was louder to the left than to the right of the sternum. A soft systolic murmur was heard at the apex. No masses or organs were felt in the abdomen and the liver could not be percussed with certainty. There were no abnormalities of the extremities and the neurologic system was intact.

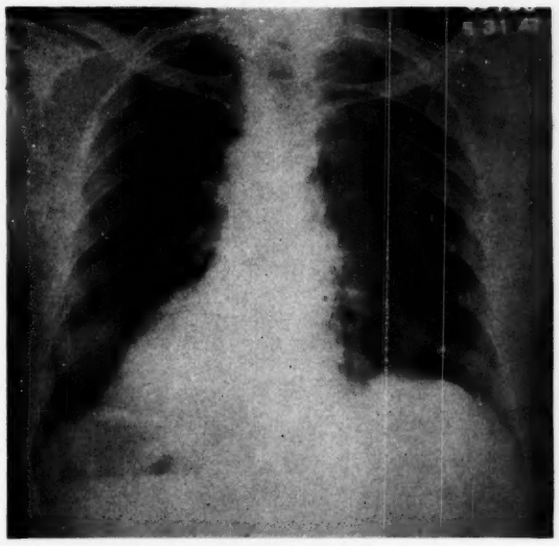

FIG. 1. Teleroentgenogram showing the heart and gas bubble in the stomach on the right.

Laboratory data were as follows: Hemoglobin was 14.6 Gm.; red blood count, 4,777,000 cells per cu. mm.; white blood count, 7,100 cells per cu. mm. with 74 per cent polymorphonuclear leukocytes. The sedimentation rate was 5 mm. in one hour corrected (Wintrobe). The Kline and Mazzini reactions were negative. The blood non-protein nitrogen was 42 mg. per 100 cc.; blood urea nitrogen was 19.3 mg. per 100 cc., giving a urea ratio of 45.9. The van den Bergh test showed no elevation. Serum cholesterol was 250 mg. per 100 cc. The kidney function, as measured by the phenolsulfonphthalein excretion test, revealed 73 per cent excretion of the dye in two hours with 40 per cent excreted in the first half hour. The urinalysis was normal. A teleroentgenogram (Fig. 1) showed the heart to be enlarged to the right and the aorta was elongated and tortuous. The lungs presented increased perivascular markings and thickening of the pleura at the left apex. The diaphragms were clear and the gas bubble in the stomach was on the right. The findings were interpreted as consistent with congenital dextrocardia and situs inversus viscerum.

The electrocardiogram (Fig. 2) showed normal sinus rhythm at a rate of 76 per minute, a P-R interval of 0.19 seconds and a QRS interval of 0.12 seconds. Inversion of P_1 was present with the arm lead wires in normal position. When the arm lead wires were reversed, S_1 and S_2 were widened and slurred. T_1 and T_2 were upright and T_3 inverted. Precordial leads, V_1 through V_6, taken over the right side of the

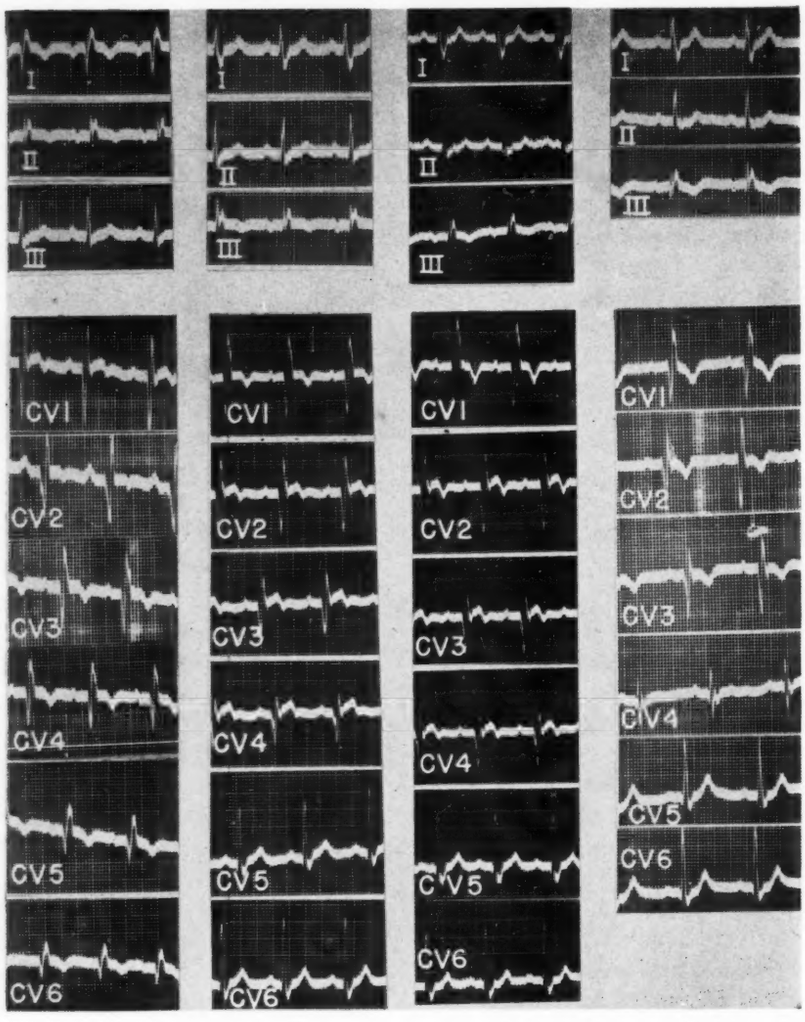

FIG. 2. A, electrocardiogram taken on admission with the arm wires correctly placed and the precordial leads taken over the left side of the chest. B, record taken the same day with the arm lead wires reversed and the precordial leads taken over the right side of the chest. C, repeat of the record five days later with the arm lead wires reversed and the precordial leads taken over the right side of the chest. D, record taken one month later.

chest showed deep Q_1, Q_2, Q_3 and Q_4; T_1 was inverted; T_2, T_3 and T_4 were diphasic; T_5 and T_6 were upright. There was minimal elevation of the RS-T segments in positions 2 and 3. The findings were considered to be consistent with congenital dextrocardia complicated by antero-septal infarction. Precordial leads taken over the left side of the chest showed a difference in tracings from position one and two while the remainder of the leads resembled those taken from position two except for a difference in voltage. A repeat of the electrocardiogram five days later revealed no significant change in the limb leads. In the precordial leads T_1 was more deeply inverted; the RS-T segment in lead II was less elevated with T_2 more inverted; T_3 and T_4 showed a slight increase in the depth of late inversion.

The patient remained in the hospital for fifteen days at bed rest and was afebrile during this period. There was no change in his blood pressure and no further episodes of pain were noted. During the first six hospital days he received 30 mg. of papaverine hydrochloride every four hours.

The sedimentation rates repeated on the sixth, tenth and thirteenth hospital days were 22, 20 and 30 mm. in one hour corrected (Wintrobe), respectively. The white blood counts repeated on the same hospital days were 8,700, 8,000 and 8,200 cells per cu. mm. On the fifteenth hospital day he was discharged to

lead a bed-chair existence with bathroom privileges for one month and then to resume gradually a program of limited activity.

The patient was seen again on July 10, 1947. His course at home had been uneventful. During the preceding week he had had one episode of substernal pain, related to effort, which had lasted about five minutes but which was promptly relieved by rest. On re-examination his blood pressure was 150 mm. Hg systolic and 100 mm. Hg diastolic. The remainder of the physical examination was unchanged. An electrocardiogram showed no change in the limb leads. In the precordial leads T_1 was more inverted; the RS-T segments in leads II and III were isoelectric with deeper inversion of T_2 and T_3; T_4, T_5 and T_6 were slightly more upright. X-rays of the gallbladder revealed rather poor concentration of the dye but contraction was satisfactory after the fatty meal. No stones were seen. The Weltmann coagulation band was 3 and the sedimentation rate was 19 mm. per hour (Westergren).

SUMMARY

The case record of a seventy-three year old man with congenital dextrocardia and situs inversus viscerum complicated by hypertension, coronary artery disease and myocardial infarction is presented. Electrocardiographic recordings of the limb leads, with and without reversal of the arm lead wires, and of the precordial leads of the V series derived from both right and left chest areas are presented. In this instance the electrocardiographic findings in precordial leads taken over the right chest point to fresh anteroseptal infarction; those leads recorded from the left chest were not informative. This serves to emphasize the fact that precordial leads should be recorded from the right side of the chest rather than the left in order that the exploring precordial electrode may overlie the area of cardiac damage, and thus manifest maximal changes in the electrocardiogram. We agree that the electrocardiogram may best be interpreted by application of the usual criteria to the limb leads taken with the arm lead wires reversed although in this case the limb leads yielded no information of diagnostic significance.

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Bromsulfalein Reaction*

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SINCE the development of the bromsulfalein liver function test by Rosenthal and White in 1925, serious reactions to bromsulfalein (phenoltetrabromphthalein) have been so rare that we can find no reports in medical literature of their occurrence. That such reactions may occur is shown by the following case report:

CASE REPORT

M. M., a thirty-five year old housewife, was admitted to the Mary Hitchcock Memorial Hospital on December 19, 1946, for evaluation of recent weight loss and allergic reactions. She had been well until March, 1942 when she was hospitalized for a miscarriage. She made an uneventful recovery, but while still in the hospital had her first episode of bronchial asthma. Prior to this she had had no known allergies. Subsequently, she continued to have recurrent asthmatic attacks of moderate severity which were always worse in the spring and fall and immediately preceding her menses. During the three months before the present admission the attacks had become increasingly severe. Previous skin tests showed multiple sensitivities to food, dust and animal furs, but not to pollens. During the six weeks before admission she had become increasingly weak, easily fatigued and had lost 20 pounds. Her past history and family history were essentially negative. There was no family history of allergy or tuberculosis. Systemic review was non-contributory.

Physical examination revealed a small, thin, pale female. She weighed 85 pounds and was 61 inches tall. The blood pressure was 125 systolic and 85 diastolic. The radial pulse was 80 and the oral temperature was 99°F. The mucous membranes of the nose were swollen. There were wheezes and rhonchi throughout both lungs. The expiratory phase was prolonged. The liver edge, felt at the level of the umbilicus, was sharp, firm and nontender. All other physical findings were normal.

Examination of the urine was negative. The hemoglobin was 15 Gm. (oxyhemoglobin—Klett Sommerson) and red blood cell count was 4,880,000. The white blood cell count was 5,200 with 40 per cent segmented neutrophiles, 51 per cent lymphocytes and 9 per cent eosinophils. The blood serologic test for syphilis by the Mazzini method was negative. X-ray of the chest was negative. An excretory urogram was normal. Two sputum specimens were negative for acid-fast bacilli, and the first and second strength tuberculin tests (P.P.D.) were negative. The non-protein nitrogen was 27 mg. per cent; the total serum protein was 5.2 Gm. per cent, with 3.4 Gm. per cent albumin and 1.8 Gm. per cent globulin. The serum cholesterol was 192 mg. per cent. The basal metabolic rate was −2 per cent and −6 per cent. Direct examination and culture of the stool were negative for pathogens.

An extensive allergy investigation revealed multiple sensitivities by the skin test method in all series, with most marked reactions to horse serum 1:100, beef 5,000 units per cc., pork 5,000 units per cc. and lamb 5,000 units per cc.

Because of the hepatomegaly, a study of liver function was initiated. The cephalin flocculation test was negative. The prothrombin time was 15.4 seconds with a control of 15.5 seconds (98 per cent of mean normal).

Bromsulfalein, 193 mg., (representing 5 mg. per Kg.) was given intravenously in approximately one minute. One minute later the patient suddenly became extremely apprehensive and sat forward gasping for breath. Breathing became increasingly difficult and labored; marked cyanosis appeared and the patient lost consciousness. Because she appeared in extremis, 1 cc. of epinephrine hydrochloride 1:1,000 was given intravenously. As there was no response 0.25 Gm. of aminophylline was given intravenously. Her face became ashen and the dependent parts of the body became deeply cyanotic; the veins of the arms and the neck were distended. Respirations were rapid and

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shallow. The same dose of aminophylline was repeated intravenously and an oxygen mask was applied. At this time the patient became completely apneic and remained so for three minutes. Artificial respiration was administered and oxygen therapy was continued. Spontaneous breathing began again and was accompanied by a severe, generalized clonic convulsion. A mixture of oxygen and helium was then given by mask and 30 Gm. of sodium succinate[1] were given intravenously. Following this, the patient began to have transitory periods of improved color alternating with periods of marked cyanosis. Gradually the patient's color improved; her respirations became normal and she returned to consciousness. The entire episode lasted approximately one hour. There was no recurrence, and the patient stated that she felt very well during the remainder of her hospitalization. Following the acute episode, her lungs remained clear and she was entirely asymptomatic. No further studies were made.

She was discharged six days later on a modified elimination diet with a supplementary synthetic protein preparation. Desensitization was considered impractical in view of the multiplicity and severity of her sensitivities.

COMMENT

Before reviewing the literature on bromsulfalein it is essential to acknowledge that the reaction just described may not have been entirely due to bromsulfalein. The 1 cc. of epinephrine hydrochloride which was given intravenously may have been responsible for the events which took place subsequent to its injection. That the patient survived this dose of epinephrine is in itself remarkable.[2] Aminophylline given intravenously also may account for some of the events which transpired as serious reactions and deaths[3] have been reported from its use. The epinephrine and aminophylline, however, were administered only when the patient appeared in extremis.

Because of the extreme severity of this reaction to the intravenous administration of bromsulfalein in an individual with multiple allergies and because we were not aware of a similar reaction to this drug, a search of the literature on this subject was made.

Phenoltetrachlorphthalein was first studied pharmacologically by Abel and Rowntree[4] in 1909. It was found by them to be non-toxic when administered intravenously and to be excreted almost entirely by the liver. A test for hepatic function using this substance was first outlined in 1913 by investigators at the Johns Hopkins Medical School.[5,6] Phenoltetrachlorphthalein, however, had certain disadvantages. Following considerable investigation by Rosenthal[7] and Rosenthal and White,[8] phenoltetrabromphthalein (bromsulfalein) was found to be ideal for liver function studies. The toxicity of this substance was found to be very low. When dogs were injected with more than 100 mg. per Kg., death occurred in 50 per cent of the animals, either at once with convulsion or within two hours preceded by chills and weakness; and in one dog, 50 mg. per Kg. was found to be fatal in four hours. At autopsy no gross lesions were found and by microscopic studies the only finding was diffuse enteritis.

Although the literature is replete with papers concerning the use of bromsulfalein as a test of liver function, no reports of its toxicity have appeared since the original work.

Capps[9] observed the results of as many as 7,000 tests a month in Italy during the war. Ingelfinger[10] is using massive doses (up to 800 mg.) of the dye intravenously in his studies of hepatic circulation. Neither of them has observed a reaction as severe as the one described. Nevertheless, both mention pyrogenic reactions, sometimes associated with nausea and vomiting, six to twelve hours after the injection and lasting one to two days. They consider this to be due to impurities rather than to the dye itself. In addition, both have observed occasional mild allergic reactions associated with urticaria and asthma. Fainting has occasionally been observed, but this was considered to be on a non-specific basis.

Capps[9] suggests that caution be used in injection of the dye. One cc. (50 mg.) of the solution is slowly injected, following which an interval of a full minute is allowed to

pass to note any untoward reactions before proceeding to inject the remainder. A total of three minutes is allowed for the injection of the full amount.

SUMMARY

A severe reaction to bromsulfalein is described. Such a reaction is extremely rare and should in no way contraindicate use of this substance. A method for injection is suggested to help prevent the type of reaction described.

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Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE SOUTHERN SECTIONAL MEETING
HELD IN NEW ORLEANS, JANUARY 26, 1948

QUANTITATIVE STUDY OF STERNAL MARROW MEGAKARYOCYTES. *Philip Pizzolato, M.D., New Orleans, Louisiana.* (From the Department of Pathology, Veterans Administration Hosptal.)

Marrow megakaryocytes were counted by three methods: (1) Fuchs-Rosenthal counting chamber, (2) coverslip and (3) slide. The marrow was obtained from the sternum by aspiration. In the chamber method the marrow was mixed with double oxalate and diluted with 1 per cent acetic acid as for a white cell count. The total nucleated elements were obtained from the same dilution using the ordinary Levy chamber. For the other methods the marrow in the aspirating needle was used in making the preparations and stained with Wright's stain. The number of megakaryocytes observed among 5,000 nucleated cells was determined from the coverslip preparation. Using the slide method, the number of megakaryocytes and nucleated cells was observed in an area of 20 by 15 mm. The results obtained from the three procedures were transformed to the number of megakaryocytes per million nucleated cells.

In a series of ten normal individuals from eighteen to twenty-seven years of age the megakaryocytes varied from 152 to 345 per million cells using the chamber method. Megakaryocytes were determined by means of the three technics in eight pathologic states. The chamber method compared favorably with the slide method in four cases whereas the coverslip technic, which according to some observers usually gives a uniform distribution of cells, did not correspond with the other methods.

The chamber method using the Fuchs-Rosenthal counting chamber appears to be a rapid, uniform and accurate procedure for estimating the number of megakaryocytes in bone marrow.

EFFECT OF METHYL-BIS-(BETA-CHLOROETHYL)-AMINE ON HEMOPOIETIC FUNCTIONS OF THE MARROW. *William C. Levin, M.D., Galveston, Texas.* (From the Department of Internal Medicine, University of Texas Medical School and the Hematology Clinic, John Sealy Hospital.)

Methyl-bis-(beta-chlorethyl)-amine hydrochloride was administered to fifteen patients with diagnoses of lymphoma, bronchogenic carcinoma, synovioma and other carcinomas. In most instances the patients received two or more courses of the drug. Complete studies of the peripheral blood were made every one to three days and serial examinations of the bone marrow were made during and following administration of the nitrogen mustard.

In all but three instances there were significant changes apparent in either the peripheral blood or the bone marrow. Two patients who originally displayed leukemoid reactions to the primary disease reacted to the drug by a drop in the leukocyte count. Three patients showed a drop in the leukocyte count to between 3,000 and 4,000. A moderately severe leukopenia (1,500 to 3,000) became evident in three patients and there were four patients in whom the leukocyte count dropped to below 1,000. In these four patients the thrombocyte level dropped to below 100,000. The bone marrow responded by displaying a moderate to marked hypocellularity after treatment was instituted. There was a close correlation between the degree of hematocytopenia in the peripheral blood and the severity of the marrow hypocellularity. In general the severity of depression of hemopoiesis was dependent upon the amount of drug administered.

In spite of severe hematologic reactions these patients displayed few clinical manifestations of leukopenia and in most instances complete hematologic remissions apparently developed after the drug was stopped.

EVIDENCE ON THE ORIGIN OF LEIOMYOMA OF THE SKIN OBTAINED BY PHARMACOLOGIC STUDIES. *William J. Senter, M.D. (introduced by M. Michael, M.D.), Atlanta, Georgia.* (From the Department of Medi-

cine, Emory University School of Medicine and the Medical Service, Grady Hospital.)

A case of multiple leiomyomas of the skin is presented. The sensitivity of these tumors to cholinergic drugs and their distribution within the area supplied by the cervical sympathetic nerves is considered conclusive evidence of their origin from smooth muscle tissue of sweat glands. It is thought that this is the only case of leiomyomas of the skin in which the site of origin of the tumors was from smooth muscle tissue deposit in the skin.

NEW METHOD FOR THE SURGICAL TREATMENT OF CARCINOMA OF THE LOWER TRACHEA AND CARINA. *Osler A. Abbott, M.D., Atlanta, Georgia.* (From the Department of Surgery, Emory University, School of Medicine.)

In the handling of carcinoma of the right upper lobe orifice it has become increasingly evident that some method allowing removal of the lower lateral wall of the trachea, carina and upper medial wall of the contralateral wall of the main stem bronchus will be necessary. This is indicated both by lesions involving this area and also in order to remove adequate area of normal tissue beyond the neoplastic lesions, especially in patients in whom the right upper lobe orifice arises either in the lower tracheal wall or in close proximity to the carina.

A new method allowing removal of these areas with primary re-establishment of continuity of the breathing tube is presented. Experiences encountered in six patients with their follow-up reports to date are discussed. Considerable attention is paid to the maneuvers necessary to allow one to keep the lower trachea open for varying periods of time in repair of such defects associated with the removal of these lesions. Attention is paid to the basic experimental work of Rollin Daniel, relative to these lesions.

THE SPATIAL VECTORCARDIOGRAM IN NORMAL MAN. *John P. Conway, M.D.* and *James A. Cronvich, M.S.,. New Orleans, Louisiana.* (From the Department of Medicine and of Electrical Engineering, Tulane University, and Charity Hospital.)

The spatial vectorcardiogram is a record of the resultant manifest potentials of the heart represented as a vector function of time.

The regular tetrahedron was employed as the reference system. Einthoven's triangle was the frontal plane. The posterior electrode position was just to the left of the tip of the seventh dorsal vertebral spine. The cathode-ray oscillograph and a camera were used for recording.

The subjects were sixteen normal male medical students. Projections of the vectorcardiogram on a mid-sagittal plane and on the frontal, superior, right and left surfaces of the tetrahedron were recorded.

$\hat{E}$ *P-Loop.* The axis is directed downward, slightly forward and to the left. The inclosed area faces upward, forward and to the left. Traced counterclockwise as viewed from the front it is of irregular contour.

$\hat{E}$ *QRS-Loop.* The axis is directed downward, slightly forward and to the left. The inclosed area faces upward, forward and to the right. A smooth ellipse-like figure whose width is less than one-third of its length, it is traced clockwise as viewed from the front, slowly at first, faster throughout the major portion and slowly again near its terminus.

$\hat{E}$ *T-Loop.* The axis is directed downward, forward and to the left. The inclosed area faces upward, forward and to the right. It is a very narrow ellipse-like figure, traced clockwise as viewed from the front, slowly in the efferent, faster in the afferent portion.

Relative axis magnitudes of the $\hat{E}$ P-, $\hat{E}$ QRS- and $\hat{E}$ T-loops are 1:10:2.

RELATIONSHIP OF THE PRECORDIAL ELECTROCARDIOGRAM TO THE ELECTRICAL FIELD OF THE HEART. *Robert P. Grant, M.D., Atlanta, Georgia.* (From the Departments of Medicine and Physiology, Emory University School of Medicine.)

The ventricular deflections of the precordial leads have been assumed to be produced predominantly by that portion of the myocardium directly beneath the electrode. In order to test this concept the extent to which the precordial deflections represented projections of the spatial cardiac vectors was studied in one hundred subjects. The three dimensional characteristics of the QRS and T vectors were determined by vector analysis of potential differences measured between four remote, electrically equidistant

electrodes on the body. The distribution of positive and negative deflections and the zones of transition for the precordial QRS and T deflections at the fourth interspace and other thoracic levels were then compared with those anticipated for them from the size and direction of the spatial vectors. In addition the precordial deflections were compared with the results from an equation which defined the surface pathway of the transitional zone for a vector of any given direction at the center of a regular ellipsoidal cylinder. There was close agreement in these regards between the precordial ECG and the spatial vectors in the patients studied. Thus, for precordial leads the heart roughly resembles a single central dipole as has already been demonstrated for the limb leads. The magnitudes of the precordial deflections increased, of course, when the electrode was nearer the heart but this appeared only to magnify the anticipated direction of the deflection. In normal subjects the transitional pathway of the QRS deflection crossed the left precordium; this was less commonly true of the transitional T pathway. The more abnormal the ventricular gradient the more disparate became the pathways; in spite of this, in most abnormal patterns both the QRS and T pathways crossed the left precordium and therefore the precordial electrode positions now in general use demonstrated transitional deflections in most instances.

VENTRICULAR GRADIENT IN HYPERTHYROID CONDITIONS. *Robert B. Failey Jr., M.D.* and *Albert L. Hyman, M.D.* (*introduced by Johnson McGuire, M.D.*), *Cincinnati, Ohio.*

In a study of the effect of hyperthyroidism and of thyroid extract on the heart the electrocardiograms of a group of patients were analyzed by study of their ventricular gradients. These cases were of two groups, the first composed of fourteen patients with hyperthyroidism and the second of eleven normal subjects to whom 6 gr. of thyroid extract were administered daily. All patients studied were free of complicating diseases and all had electrocardiograms that were normal except for a few instances in which transient abnormalities of cardiac rhythm were noted.

In the group with hyperthyroidism all of the fourteen patients showed an increase in the magnitude of their ventricular gradient as compared with control electrocardiograms taken after remission of the disease induced by surgery or by thiouracil. This increase averaged 39 per cent, with a range from 4 to 100 per cent. In addition seven of this group showed a significant clockwise shift in the direction of the ventricular gradient, averaging 26 degrees with a range of plus 16 to plus 48 degrees. The other seven patients in this group showed no significant shift in the direction of the gradient.

In the group receiving thyroid extract all of the eleven subjects showed an increase in magnitude of the ventricular gradient. This magnitude averaged 30 per cent with a range from 7 to 73 per cent. None of these patients showed a significant shift in the direction of the gradient.

In both groups of patients increase in heart rate was a common occurrence, and values obtained for magnitude and direction of ventricular gradients were corrected for changes in heart rate.

It is suggested that the increased magnitude of the ventricular gradient is a reflection of the increased work of the heart. It is also suggested that the shift in the direction of the gradient in the hyperthyroid group may indicate myocardial strain since this finding has been previously noted in patients with hypertension and acute glomerulonephritis.

ACQUIRED DEFECT OF THE SEPTUM INTERVENTRICULORUM AS A SPECIAL FORM OF MYOCARDIAL RUPTURE COMPLICATING CORONARY ARTERY DISEASE WITH MYOCARDIAL INFARCTION. *Robert H. Furman, M.D.* and *George R. Meneely, M.D., Nashville, Tennessee.* (From the Department of Internal Medicine, Vanderbilt University, School of Medicine.)

The authors' interest in this uncommon but not rare event following myocardial infarction was stimulated by its occurrence in a patient under their observation. The literature was reviewed and fifty-four reports noted and studied. Two cases from the authors' experience are added and clinical and pathologic observations made. Septal rupture is compared to cardiac rupture in general. Twenty per cent of seventy-six cases of cardiac rupture noted in a series of 28,657 autopsies showed septal rupture. The clinical picture is that of interventricular septal defect superimposed on that of myocardial infarction. The systolic murmur is generally

loudest in the fourth or fifth interspace close to the sternum. Two patients exhibiting diastolic murmurs had large septal tears. The average interval between infarction and cardiac rupture or septal rupture was seven days. Death following cardiac rupture occurs almost always within a few hours. The duration of life following septal rupture is considerably longer. One patient lived almost five years. Twenty per cent of the patients in whom ECG studies were made showed right axis deviation and 25 per cent showed some form of block. The site of septal perforation is almost always at or near the apex, in contrast to the congenital defect which is generally at the base.

ANOXIA PRODUCES MYOCARDIAL LESIONS IN DOGS. FURTHER EVIDENCE OF THE PART PLAYED BY CAPILLARIES IN THE PATHOGENESIS OF MYOCARDIAL INJURY. *Robert G. Gale, M.D., Robert H. Furman, M.D., Janet M. Lemley, M.D., Ira T. Johnson, Jr., M.D., Thomas F. Parrish, M.D.* and *George R. Meneely, M.D., Nashville, Tennessee.* (From the Department of Medicine, Vanderbilt University School of Medicine.)

Previous work from this laboratory has shown that asphyxia and local ischemia adversely affect the myocardial capillaries. The present report extends these findings by demonstrating that anoxia alone can produce myocardial capillary injury.

Fifty-one dogs were used. Room air was diluted with nitrogen in large spirometers to an oxygen concentration of 5 to 10 per cent. A tracheal T cannula was inserted and the lungs ventilated with a pump using an open circuit. Arterial oxygen saturation was measured with the Van Slyke manometric apparatus and for the most part ranged from 30 to 50 per cent saturation. In successful experiments the anoxic period was usually three or four hours although some hearts showed injury in a shorter time. In some dogs electrocardiographic records were taken. Trypan blue was used in twenty-three dogs while the remaining twenty-eight did not receive it. Only twenty-five experiments were "successful" in the sense that a prolonged period of anoxia was achieved.

Striking lesions were found in the gross in eleven dogs while questionable lesions were seen in four more. Their distribution was patchy. No large areas comparable to some obtained under asphyxia occurred. The gross changes were more striking than the microscopic except in cases of marked hemorrhagic alteration. Trypan blue is an anticoagulant and definite lesions were more frequent when it was administered, but the possibility remains that lesions with trypan blue are more readily detected.

The pathologic character of the lesions ranged from edema through protein-containing edema fluid with slight hemorrhage to marked hemorrhagic alteration. Electrocardiographic changes were rarely seen, probably due to strictly intramyocardial location of some lesions, their small size or their patchy distribution.

NODES OF CONTRACTURE IN STRIATED MUSCLE. *Janet M. Lemley, M.D.* and *George R. Meneely, M.D., Nashville, Tennessee.* (From the Department of Medicine of Vanderbilt University, School of Medicine.)

The usual form of contraction in striated muscle respects the architecture of the fiber and involves only the individual myofibrillar elements of the Q stripe. There is another, probably atavistic, mechanism called "Schrumpfkontraktionen" by Exner. One of the authors in a previous work produced these *in vivo* and reported on their nature. Nodes of contracture can be produced which are localized, nonpropagated, slow compared to the twitch response, reversible when the stimulus is appropriate and irreversible when the stimulus is excessive. In their reversible form they resemble morphologically normal smooth muscle contractions while in their irreversible form they are identical with Zenker's hyaline degeneration of muscle.

Evidence is presented that this form of contraction occurs in humans as myo-edema. Acutely ischemic regions of dog hearts also exhibit this phenomenon and there is suggestive evidence that it may play a part in angina pectoris and in the SFT shifts in the electrocardiogram derived from ischemic areas.

USE OF A HYPERACTIVE CAROTID SINUS AS A POSSIBLE AID IN THE DIAGNOSIS OF CORONARY ARTERY DISEASE. *R. Bruce Logue, M.D.* and *Robert L. Whipple, M.D., Atlanta, Georgia.* (From the Emory University Hospital, Emory University.)

The characteristic electrocardiographic changes of myocardial infarction are prevented by the presence of left bundle branch block since the initial negativity of the left ventricle is replaced by positivity. This is due to transeptal activation of the blocked ventricle from right to left. Thus, the diagnostic changes in the QRS and T waves cannot occur. On occasion the conducting pathways are incompletely damaged so that transient or intermittent bundle branch block may occur. During the period of normal intraventricular conduction the changes due to coronary artery disease may be apparent, only to disappear with recurrence of bundle branch block. When the conducting pathways are only partially damaged, normal conduction may at times occur when the sino-auricular rate is slowed. This is presumably due to the longer refractory period of the muscle which allows the damaged tissue to recover sufficiently to conduct the excitatory process. There may be in any given individual a critical rate above which the bundle will not conduct and below which normal conduction occurs. Normal intraventricular conduction has been established in such instances by administration of ergotamine tartrate intravenously which produces reflex slowing through its sympatholytic action. It might be expected that in the presence of an irritable carotid sinus a similar result would occur. Such an example was noted in the present case in which left bundle branch block occurred with the onset of myocardial infarction. The presence of an irritable carotid sinus allowed the underlying changes associated with coronary disease to be recorded. Each of the standard and six precordial leads were taken before, during and after carotid sinus pressure and the effect of various autonomic drugs was studied.

EFFECT OF VASOCONSTRICTIVE AND HYPERVOLEMIC MEASURES UPON TETRAETHYL AMMONIUM ORTHOSTATIC HYPOTENSION. *A. Ruskin, M.D.* and (*by invitation*) *H. Roosth, M.D.* and *H. B. Griffin, Galveston, Texas.* (From the University of Texas Medical Branch.)

We have previously reported the finding of orthostatic hypertension in various clinical states in which vasodilatation seemed to play a prominent part (*Proc. Am. Fed. Clin. Research*, 3: 44, 1947). Among the conditions previously and recently observed to be associated with orthostatic hypotension of various degrees have been acute and severe chronic anemias, other blood dyscrasias, hyperthyroidism and alcoholism. Both ephedrine and desoxycorticosterone were observed by us to prevent in various degrees the orthostatic phenomenon.

Tetraethyl ammonium uniformly produced orthostatic hypotension in doses of 0.2 Gm. to 0.5 Gm. intravenously. In some patients we observed relative hypertension in the recumbent position, a phenomenon also often observed in clinical orthostatic hypotension. With a dose of 0.5 Gm., orthostatic syncope was common, with marked hypotension and tachycardia. The effects were less or gone within thirty minutes in the majority of cases.

Tetraethyl ammonium regularly decreased the circulating blood volume (Evans blue method). While preliminary injections of paredrine (30 to 60 mg.), ephedrine (50 mg.), plasma (750 to 1,000 ml.) and desoxycorticosterone (20 to 40 mg. plus 10 gm. of NaCl) increased the blood volume, subsequent tetraethyl ammonium injections produced variable results. In some cases orthostatic hypotension and tachycardia were prevented, in others they were not. Likewise, the drops in circulating blood volume following tetraethyl ammonium were prevented in some cases, particularly by preliminary paredrine and plasma. As in clinical cases venous pressures and circulation times in the recumbent and upright positions were apparently not affected by "etamon" orthostatic hypotension short of syncope.

"ALBUMIN-ADDITION" TEST. *F. Homburger, M.D., Edward S. McCabe, M.D., N. F. Young, M.D.* and *Edward C. Reifenstein, Jr., M.D., New York, New York.* (From the Department of Clinical Investigation, the Sloan-Kettering Institute for Cancer Research, Memorial Cancer Center.)

Intravenous administration of 75 Gm. of human albumin in normal subjects and in patients with hypoproteinemia causes a temporary rise in the concentration of albumin. Return of the albumin level to the pre-injection value is not as rapid as normal in some patients with hypoproteinemia. The significance of these differences in the rate of disappearance of the injected albumin are discussed, particularly in

relation to the various etiologic factors that lead to hypoproteinemia.

"PROTEIN-SUBTRACTION" TEST. *F. Homburger, M.D., N. F Young, M.D.* and *Edward C. Reifenstein, Jr., M.D., New York, New York.* (From the Department of Clinical Investigation, the Sloan-Kettering Institute for Cancer Research, Memorial Cancer Center.)

Removal of circulating protein by plasmapheresis in normal subjects is followed by a moderate fall in the serum protein level at twenty-four hours and by a prompt restoration to the pre-injection value or higher at forty-eight hours. In some patients with hypoproteinemia the depression of the serum protein level is considerably greater than normal at twenty-four hours, and return of the protein level to the pre-injection value is not as rapid as normal. The significance of these differences in the degree of depression and in the rate of restoration of circulating protein after acute withdrawal are discussed, particularly in relation to the various etiologic factors that lead to hypoproteinemia.

QUANTITATIVE STUDIES OF HUMAN LIVER GLYCOGEN. *Philip K. Bondy, M.D.* and *Walter H. Sheldon, M.D., Atlanta, Georgia.* (From the Departments of Medicine and Pathology, Emory University School of Medicine, and Grady Hospital.)

Although numerous analyses of liver glycogen in animals have been recorded, few such observations have been made in humans. It seemed desirable to determine liver glycogen concentrations in humans and to correlate these with the findings in animals. Serial human liver biopsy specimens have been obtained by needle biopsy and stained with Gomori's test for glycogen. It has been shown that the optical density of the stained slides, determined photometrically, is directly correlated with the liver glycogen content determined by the method of Good, Kramer and Somogyi. This correlation permits quantitative determination of the glycogen content of the liver by photoelectric densitometer readings from the histologic preparation.

The technic has been applied to four patients with diabetic acidosis. In three, in whom acidosis was severe, the initial glycogen content ranged from 0.20 to 0.28 per cent. After treatment the glycogen content was increased until at seven hours it was normal (4.35 per cent). In one patient with mild acidosis the liver glycogen content before treatment was 2.30 per cent.

Three normal fasting patients have shown glycogens ranging from 2.36 to 4.25 per cent. After breakfast the glycogen content was increased. One patient fasted for thirty-six hours. Her initially normal glycogen level (3.20 per cent) decreased progressively to a low of 1.85 per cent, at which time her serum acetone level was 20 mg. per 100 ml. and her urine acetone negative.

These findings suggest that in certain respects the human liver glycogen response pattern may be somewhat different from that of the animals commonly used for experiments on carbohydrate metabolism.

GRAMICIDIN DERIVATIVES. *Godfrey E. Mann, M.D.* and *Otto Schales, M.D., New Orleans, Louisiana.* (From the Department of Biochemistry, Tulane University and Chemical Research Laboratory, Alton Ochsner Medical Foundation.)

Gramicidin, a potent antibiotic agent, has not been employed systemically because of its high toxicity and its hemolytic properties. A number of derivatives of this substance were prepared which were considerably less toxic and hemolytic than the starting material but retained an appreciable antibacterial activity. Some of the reagents employed for this purpose were sodium hydroxide, iodine, hydroxylamine, hydrogen chloride in glacial acetic acid and hydrogen peroxide. The reactions of gramicidin with these substances were carried out under mild conditions to avoid excess degradation of the polypeptide molecule. Hemolytic activity was measured by allowing the various derivatives to act upon a suspension of washed human red cells in isotonic saline. Progress of the hemolysis was determined periodically by a turbidimetric procedure. Bacteriostatic tests were performed by incubating standard dilutions of the test organisms with various concentrations of the derivatives and estimating turbidimetrically the concentration required to inhibit growth by 50 per cent. Toxicity data were obtained using white mice as test animals. The various derivatives had from 1 to 0.1 per cent of the toxicity of gramicidin when given intravenously. Their bacteriostatic activity was from

20 to 90 per cent of that of gramicidin. The hemolytic activity of the various gramicidin derivatives in isobacteriostatic concentrations was 7 to 20 per cent of that of the starting material. Both human and bovine plasma had an inhibitory effect on hemolytic and bacteriostatic activities of gramicidin and its derivatives. This effect is predominantly due to the globulin fraction IV-1; crystalline bovine albumin did not reduce the bacteriostatic and hemolytic properties of gramicidin and its derivatives.

SIGNIFICANCE OF RECURRENT POSITIVE BLOOD CULTURES IN PATIENTS WITH BACTEREMIA AND ENDOCARDITIS DURING THERAPY WITH PENICILLIN. *Harold L. Hirsh, M.D., Harry F. Dowling, M.D.* and *Jay A. Robinson, M.D., Washington, D. C.* (From the Department of Medicine, Georgetown University, School of Medicine.)

Although resistance to penicillin has been induced in strains of penicillin-sensitive bacteria *in vitro*, there are few reports on increased resistance *in vivo* during treatment.

Of fifty-five patients with endocarditis and bacteremia treated with penicillin eleven had a recurrence of a positive blood culture during therapy. In each instance the causative organisms were found to be more resistant to penicillin. In seven patients, two with staphylococcic bacteremia, three with staphylococcic endocarditis and two with Streptococcus viridans endocarditis, this was accompanied by a return of symptoms of active infection. The increase ranged from 4- to 2048-fold. Three strains exhibited increases on one occasion, one on two, one on three and two on four occasions. The blood penicillin concentrations were determined in six patients after the appearance of organisms with increased resistance. Since it is established that in patients with endocarditis blood levels four to eight times the *in vitro* sensitivity of the causative organisms are required, none of these patients can be considered as having had an adequate level. The dose was increased in all the patients and recovery followed in four, one died of overwhelming infection, another was ultimately cured with streptomycin and another died of debility with no evidence of active infection. In the other four patients, one each with staphylococcic and Str. viridans endocarditis and two with staphylococcic bacteremia, the bacteriologic findings were not accompanied by symptoms of active infection. The increases ranged from 2- to 4-fold. Adequate blood concentrations of penicillin were found in the two patients in whom they were determined. The dose of penicillin was continued and the patients recovered.

The significance of these bacteriologic findings is discussed. It has been observed that an occasional organism will manifest as much as an 8-fold change in sensitivity to penicillin spontaneously or as a result of the inaccuracy of the method. It is believed, however, that the increases in resistance to penicillin observed in the seven patients represent true changes in penicillin sensitivity. The significance of the increased resistance in the other four patients is unknown.

STREPTOMYCIN IN THE TREATMENT OF PERTUSSIS. *Jerome L. Kohn, M.D.* and *Lewis W. Wannamaker, M.D., Durham, North Carolina.* (From the Department of Medicine, Duke University.)

One hundred twenty-nine patients with pertussis were treated with streptomycin at the Willard Parker Hospital in New York City; one hundred of these were infants under one year of age. On admission, eight patients were classified as mild, ninety-six as moderate and twenty-five as severe. Streptomycin was administered by one of three routes; (1) as an aerosol, (2) intramuscularly or (3) as nose drops. Aerosol treatments were given to young infants by means of a small plastic oxygen hood. Eight patients who were considered critically ill were given hyperimmune human pertussis serum in addition to the streptomycin. There were five deaths. In the remaining patients the subsequent clinical course was judged to be good in ninety-five, fair in twenty-seven and poor in two. Skin tests employing lyophilized pertussis agglutinogen were done on 123 patients. A positive reaction was obtained in eighty-two patients (66 per cent).

EFFECT OF SYMPATHECTOMY ON BLOOD VOLUME IN HYPERTENSIVE PATIENTS. *H. S. Mayerson, M.D.* and *W. D. Davis, M.D., New Orleans, Louisiana.* (From the Department of Physiology, Tulane University, School of Medicine and the Ochsner Clinic.)

Serial blood volume determinations were made in twenty-one patients with hypertensive vascular disease before and at intervals after sympathectomy. The follow-up period ranged from two weeks to eighteen months. In all but one patient, in whom a transthoracic approach was used, thoracolumbar sympathectomy was done. Plasma volumes were determined by the dye technic, 5 ml. of 0.5 per cent T-1824 (Evans blue) being used for injection. Optical densities were measured with the photoelectric colorimeter; dye-free plasma was used as a blank. Total circulating red cell mass was calculated from peripheral venous hematocrit and total circulating protein from the specific gravity of the plasma obtained by the falling drop method.

In this group of patients no consistent relationship between blood volume and blood pressure levels was demonstrated following operation. The most constant observation was considerable decrease in red cell mass in the early postoperative period usually accompanied by a concomitant increase in plasma volume. This was attributed to operative blood loss and was exhibited by ten of twenty patients. In some patients postoperatively there was close correlation between the blood volume changes and blood pressure response but in others there were wide divergencies. These included instances of falling blood volume and increasing blood pressure as well as the reverse.

Of the four patients who have had good blood pressure responses to operation three had high blood volumes and red cell mass values preoperatively and one was within normal range. All five patients who had poor results from sympathectomy had low circulating red cell masses and three had low total blood volumes. In general those patients with relatively advanced vascular disease tended to have low values both for circulating red cell mass and total blood volume.

Inadequacies of Propylthiouracil in the Treatment of Thyrotoxicosis.

Arthur B. Codington, M.D. and *Philip K. Bondy, M.D., Atlanta, Georgia.* (From the Department of Medicine, Emory University, School of Medicine and the Medical Service, Grady Hospital.)

In the evaluation of the therapeutic effectiveness of propylthiouracil, certain variations of response were encountered which are not generally appreciated. The therapeutic dose appears larger than is generally stated. Relapses have occurred after an initial response without altering the dose of propylthiouracil. Certain patients have proved totally refractory to large amounts of the drug.

Forty-five patients have been observed in fifty-two separate episodes of thyrotoxicosis. Twenty-nine of these patients with such episodes have been treated with propylthiouracil. The remainder have received thiouracil or a combination of thiouracil and propylthiouracil separately.

Propylthiouracil in a dose of 75 to 100 mg. per day has generally proved ineffective. Several patients on this dose initially made a partial response but subsequently relapsed despite unchanged dosage. On 150 mg. per day the results were improved but a significant number of patients still did not respond satisfactorily. Two patients relapsed under treatment with this dose. Of nine patients who did not respond satisfactorily to 150 mg., two did well on 200 mg., two required a dose of 250 mg. and one made a response only when the dose was increased to a level of 300 mg. One patient after being inadequately controlled on 300 to 350 mg. for five months has recently shown remarkable improvement on 400 mg. per day. Three patients must still be considered therapeutic failures despite intensive therapy with doses of propylthiouracil of 300 mg. or above. Only one instance of toxicity with propylthiouracil has been encountered, a case of leukopenia, which rapidly cleared upon stoppage of the drug.

In certain instances a beneficial effect has been shown with administration of iodides in conjunction with propylthiouracil.

Successful Treatment of Acute Thyroiditis with Thiouracil.

T. Haynes Harvill, M.D., Dallas, Texas.

Six patients with acute thyroiditis were successfully treated with thiouracil, with rapid and dramatic improvement in objective findings and subjective complaints. Diagnostic features of acute thyroiditis are enumerated. Mild granulocytopenia was encountered in one patient. This report supplements and confirms the experience of King and Rosellini who first advocated the use of thiouracil for acute thyroiditis.

INTESTINAL PARASITES IN PUERTO RICO. *Oscar Felsenfeld, M.D.* and *Viola Mae Young, M.S. (by invitation), San Juan, Puerto Rico.* (From the Presbyterian Hospital.)

The stool specimens of 200 natives of Puerto Rico who live in San Juan or its suburbs and who came to the clinic or were admitted to the wards of the Presbyterian Hospital of San Juan for other reasons than diarrhea, were examined with the aid of a method consisting of saline and iodine smears and flotation. Parasites were present in 144. Multiple infections were numerous. The occurrence of the parasites detected with the aid of the above method was the following: E. histolytica, 18 per cent; E. coli, 31 per cent; E. nana, 27 per cent; I. butchlii, 2 per cent; Dient. fragilis, 0.5 per cent; G. lamblia, 3.5 per cent; Ch. mesnili, 1 per cent; T. hominis, 2.5 per cent; Emb. intestinalis, 1 per cent; Enteromonas, 0.5 per cent; N. americanus, 11 per cent; A. lumbricoides, 2.5 per cent; Tr. trichiura, 19 per cent; Strong. stercoralis, 0.5 per cent; Intercapsifer, 0.5 per cent; Balant. coli, 0.5 per cent; Sch. mansoni, 0.5 per cent. Most patients infected with helminths had a low blood hemoglobin content and eosinophilia, the latter reaching as high as 51 to 53 per cent. No connection could be found between helminthic or E. histolytica infections and the occurrence of target cells which are frequently present in the blood of children and pregnant women with hypochromic anemia. The E. histolytica strains mostly belonged to the so-called "small variety" of this organism.

VALUE OF PROCTOSCOPY IN DIAGNOSIS OF AMEBIAS. *Spalding Schroder, M.D., Atlanta, Georgia.* (From the Emory University School of Medicine.)

From April 20, 1945, to August 8, 1945, 632 patients complaining of moderately severe diarrhea or dysentery were proctoscoped at an Overseas Army General Hospital. Adequate microscopic examination of their feces was also performed. A diagnosis of amebiasis was made in one hundred of these patients and it is these cases which furnished the material for this study.

Of the one hundred patients with amebiasis there were fifty in whom both positive proctoscopic findings and trophozoites were demonstrated. Twenty-seven patients had trophozoites of E. histolytica but their rectosigmoids appeared normal to proctoscopy. The remaining twenty-three patients had negative stool examinations and rectal smears, but rectal lesions were visualized that were considered typical of amebiasis. Furthermore, these twenty-three patients responded symptomatically to routine antiamebic therapy and repeated proctoscopic examinations revealed that the lesions healed normally. It is because of these findings that demonstration of the trophozoites is not considered obligatory in establishing a diagnosis of intestinal amebiasis.

Because of the high incidence of unsuspected amebiasis and the need for greater accuracy in its diagnosis, more general use of the proctoscope is recommended.

APPLICATION OF A QUANTITATIVE GONOCOCCAL COMPLEMENT FIXATION TEST TO THE DIAGNOSIS OF ACUTE POLYARTHRITIS. *Max Michael, Jr., M.D., Atlanta, Georgia.* (From the Medical Service, Lawson VA Hospital, and the Department of Medicine, Emory University School of Medicine.)

An exact etiologic diagnosis in cases of acute polyarthritis is one of the more difficult problems encountered in medical practice. In an attempt to better classify this group of patients a quantitative gonococcal complement fixation test has been investigated. This test has fallen into disrepute in many clinics in this country principally because of the uncertainty of its specificity. Realizing the vagaries of the procedure, we have attempted to maintain caution in reaching conclusions.

The soluble antigen is prepared using a modification of the method described by Price. The choice of organism for antigen is one of trial and error. The organism chosen must have wide antigenic properties and low anticomplementary powers. It has been found using the present method that a single strain is adequate and that the use of combined antigens does not increase the sensitivity of the test. Observations made thus far may be summed up as follows: (1) The test appears to be specific for gonococcal infection. Sera from patients with various types of non-gonococcal arthritis, both acute and chronic, give negative reactions. (2) Positive results are obtained in all patients with gonococcal arthritis, however, a single negative fixation test does not rule out the presence of gonococcal infection. Serial samples must be

run for probably two months from the onset of the disease before a negative test assumes significance. (3) No characteristic antibody pattern is observed in patients with gonococcal arthritis. The pattern or height of the response appears uninfluenced by the presence or absence of gonococci in the joint fluid or whether or not chemotherapy has been administered. Furthermore, no correlation is noted with the degree of activity of the joint as evidenced by pain, swelling, fever or sedimentation rate. (4) In general once a positive test reverts to negative, activity in the joint has subsided. On the other hand, it is not uncommon to have a persistently elevated titer after all other clinical and laboratory manifestations of the disease have disappeared. The results obtained with the test in the past one and one-half years are sufficiently encouraging to warrant continued investigation.

LYMPHOGRANULOMA VENEREUM OF SUPRACLAVICULAR LYMPH NODES WITH MEDIASTINAL LYMPHADENOPATHY AND PERICARDITIS. *Walter H. Sheldon, M.D., Margaret Wall, M.D., John R. Slade, M.D.* and *Albert Heyman, M.D. Atlanta, Georgia.* (From the Departments of Pathology and Medicine, Emory University, School of Medicine, and Grady Memorial Hospital.)

Isolated cases of systemic lymphogranuloma venereum have been reported but few of them have been proven by isolation of the virus of this disease. We have studied a patient with pericarditis and mediastinal and supraclavicular lymphadenopathy and isolated this virus from one of the lymph nodes.

The patient was a young Negro who was admitted because of a pericardial friction rub and roentgenographic demonstration of mediastinal lymphadenopathy. The only other significant physical finding was a single large supraclavicular lymph node. Histologic examination of this node revealed pathologic changes typical of active lymphogranuloma venereum. Hyperglobulinemia, a positive Frei test and a significantly high titer of complement-fixing antibodies for lymphogranuloma venereum were demonstrated. Another supraclavicular lymph node appeared several weeks later. Histologic examination of this also showed active lymphogranuloma venereum. A virus was isolated from this lymph node by intracerebral inoculation into mice and was identified as the agent of lymphogranuloma venereum. It seems reasonable to assume that the mediastinal lymphadenopathy and the pericarditis were also caused by this agent. Thorough studies revealed no evidence of other etiology.

The patient was afebrile and did not appear ill. The pericardial friction rub subsided spontaneously but a moderate tachycardia persisted. He has been followed for three months but no further changes have been observed.

Certain facts in connection with this case deserve emphasis. The histologic picture of this disease is often diagnostic. Lymphogranuloma venereum is a systemic disease in which the presenting manifestations may not suggest venereal origin.

Report of the Committee on Therapy of

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Hay Fever	790 CASES	304 (38%)	234 (30%)	252 (32%)
Asthma	397 CASES	119 (30%)	82 (21%)	196 (49%)
Pollen Asthma	226 CASES	73 (32%)	55 (24%)	98 (44%)
Vasomotor Rhinitis	130 CASES	20 (16%)	42 (32%)	68 (52%)
Urticaria	24 CASES	4 (17%)	8 (33%)	12 (50%)
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TOTAL	1,570 CASES			

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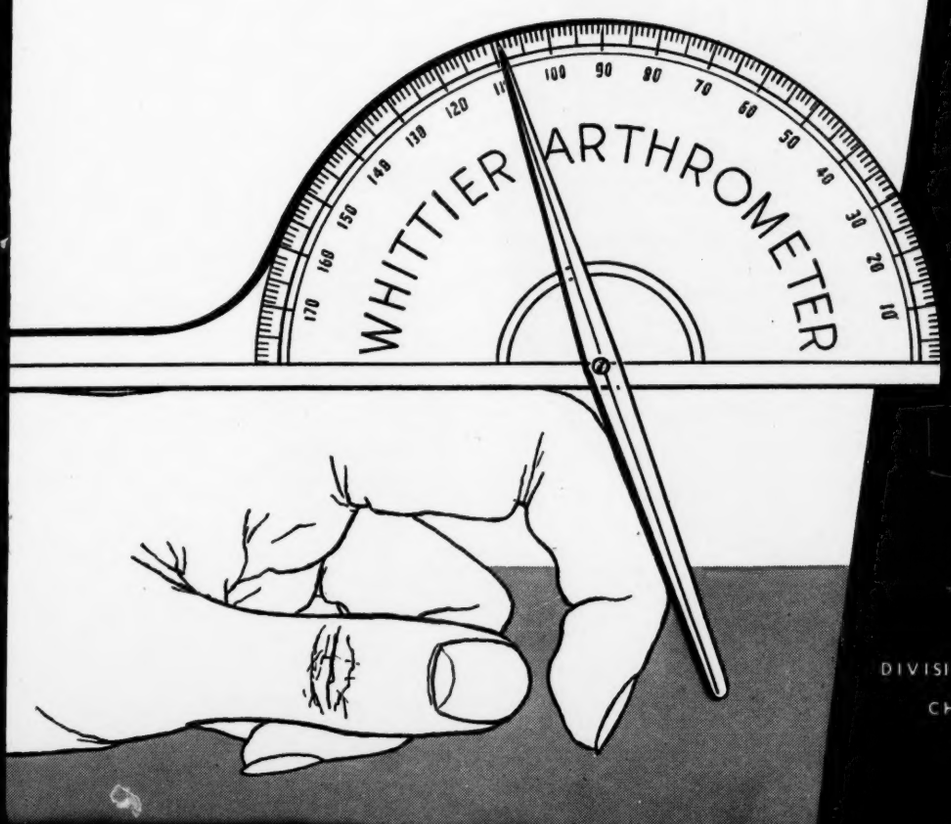

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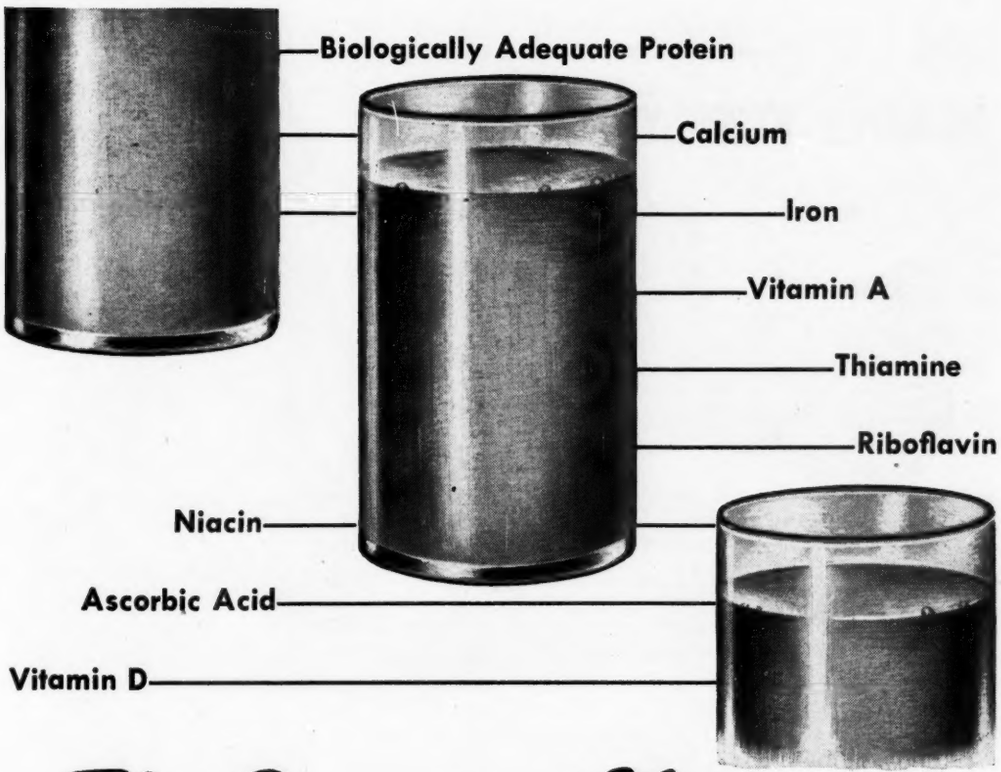

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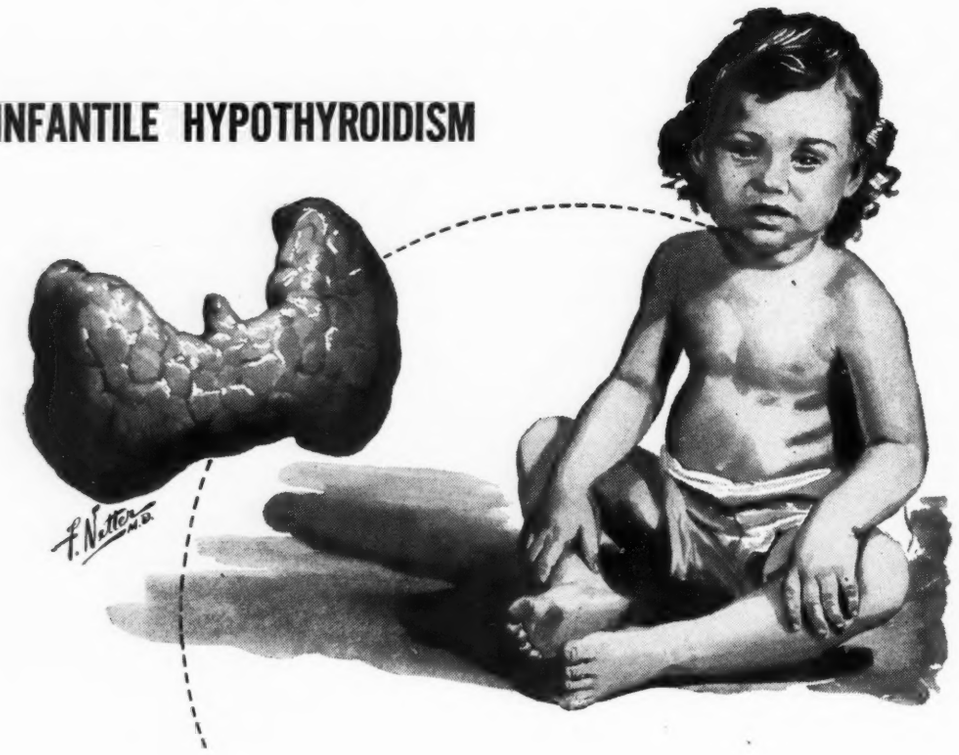

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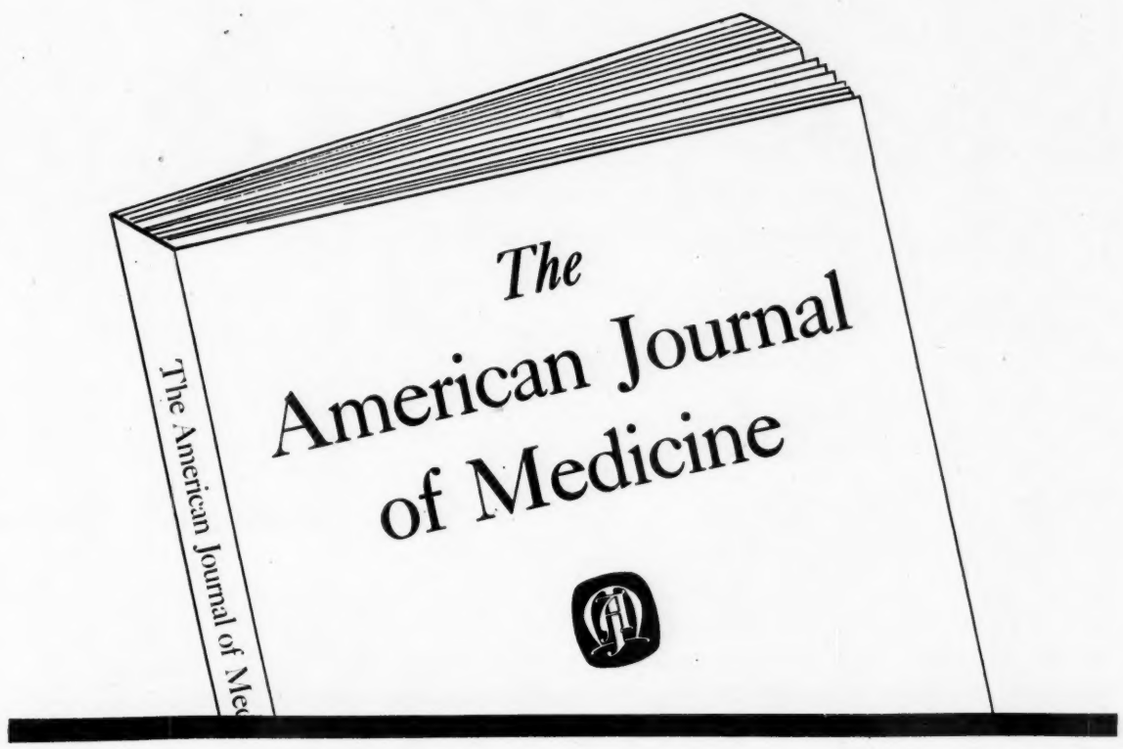

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